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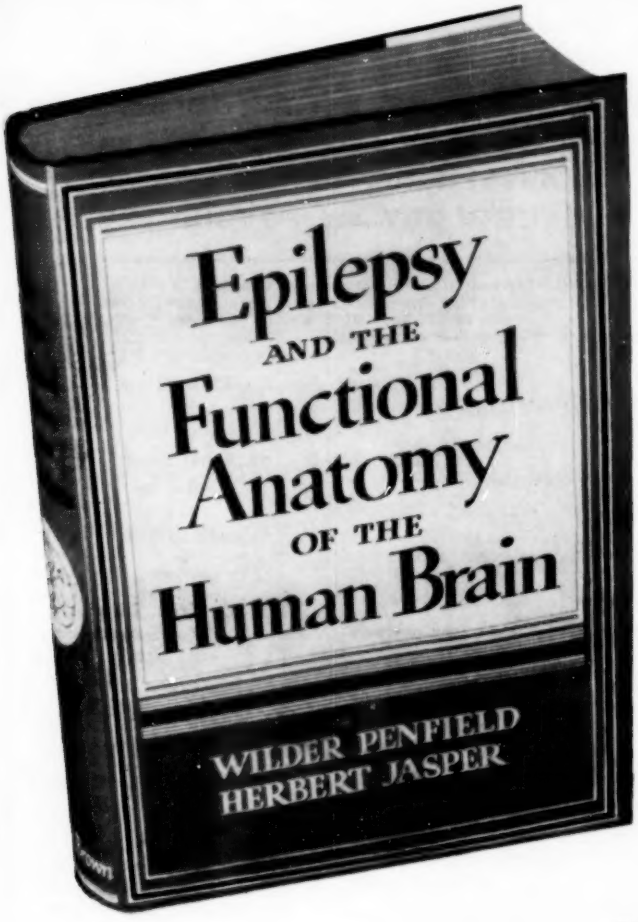

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CORTICAL ABLATIONS IN DOGS WITH CHRONIC NEUROGENIC HYPERTENSION

HERBERT C. JOHNSON, M.D.
AND
KENNETH M. BROWNE, M.D.
BALTIMORE

MANY CLINICIANS believe that psychosomatic factors are important in the pathogenesis of essential hypertension in man. If so, it is likely that "autonomic zones" of the cerebral cortex constitute, at least in part, the neuroanatomic substrate responsible for the introduction of these factors into the physiologic processes concerned with regulation of the blood pressure. Indeed, Fulton [1] has stated that perhaps the most significant disclosure of the past few years in the field of scientific medicine has been the recognition of certain cortical regions as being integral parts of the autonomic nervous system because that revelation has afforded a sound physiologic background for psychosomatic aspects of medicine.

There have been isolated reports of persistent falls in the blood pressure of hypertensive patients subsequent to various psychosurgical procedures.* Although this was not the usual result of such operations,† no deliberate effort was made to remove or undercut cortical regions demonstrated at the time of operation to have been concerned with vasomotor responses. The absence of histologic material which would allow a comparison of positive and negative results as regards the effect of psychosurgical procedures upon essential hypertension has made it impossible to determine the importance of the cerebral cortex in the maintenance of essential hypertension. This uncertainty has led other investigators to ponder the role of the cerebral cortex in the regulation of the blood pressure [11] and has engendered speculation as to the eventual development of cortical operations for the treatment of essential hypertension.[12]

The following investigation was undertaken as an experimental approach to the above problem, with full realization of the many differences which exist between essential hypertension in man and experimental types of hypertension in animals. The study concerns the effect of multiple ablations of cortical areas concerned with vasomotor regulation upon the blood pressure of dogs with chronic neurogenic hypertension.

From the Division of Neurological Surgery, The Johns Hopkins University School of Medicine.

This study was supported by grants from the American Heart Association and the Life Insurance Medical Research Fund.

* References 2 through 5.

† References 4 and 6 through 10.

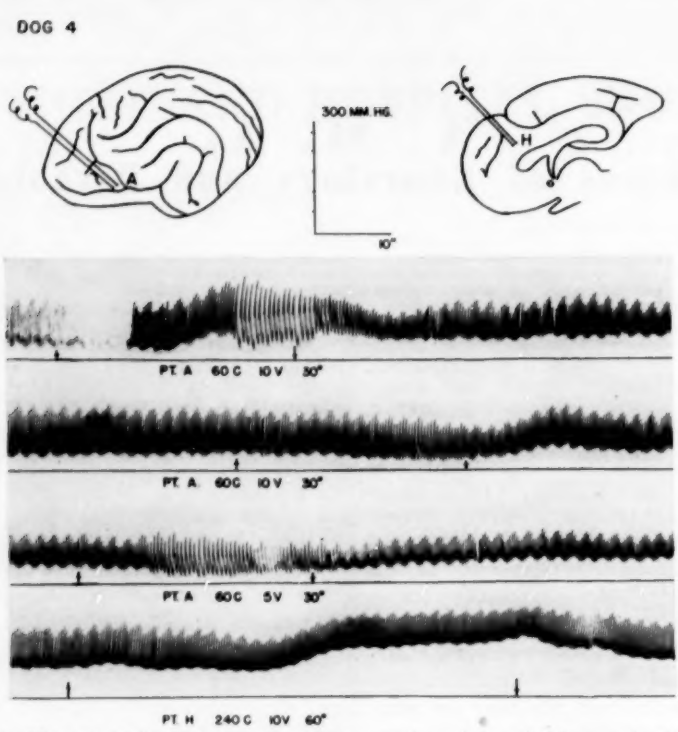

Fig. 1. (Dog 4).—Stimulation of the posterior portion of the orbital gyrus in this normotensive dog resulted in a pressor response on one occasion and a depressor response a few minutes later. The effect on the heart rate was also variable. A typical pressor response from the anterior part of the cingulate gyrus is also illustrated.

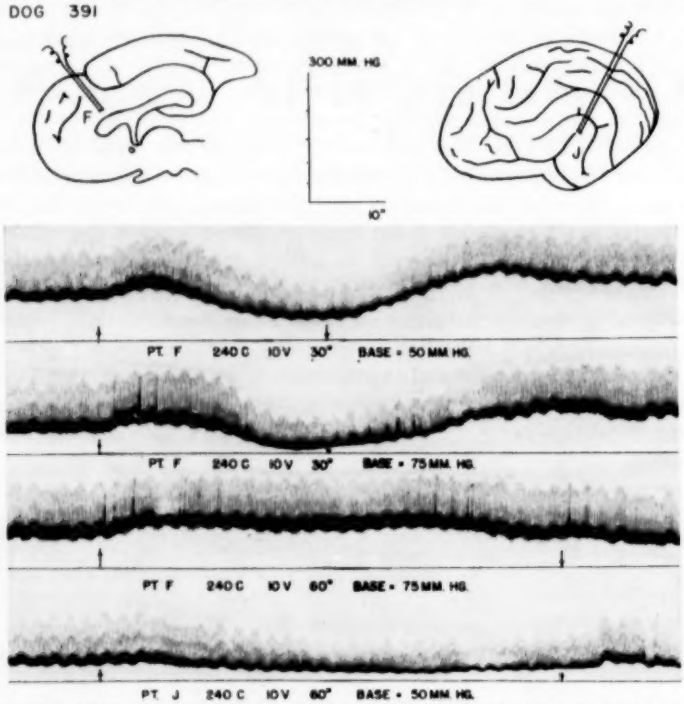
DOG 391
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Fig. 2 (Dog 391).—The variable vasomotor response obtained from the anterior cingulate gyrus even in the same animal at an interval of a few minutes is illustrated in a dog with neurogenic hypertension. A depressor response elicited from the temporal lobe is also illustrated.

METHODS

After several control blood pressure readings by percutaneous puncture of the femoral artery, neurogenic hypertension was produced in adult dogs by removing the carotid sinus bilaterally, excising a segment of the aortic depressor nerve on one side, and removing a length of the entire vagal-sympathetic complex on the remaining side. Twenty-four satisfactory preparations

Fig. 3.—The blood pressure effects of electrical stimulations of the cortex of five hypertensive dogs are illustrated in the upper figure, and in the lower figure the results in eight normotensive dogs are given. Solid dots represent rises in blood pressure of 10 mm. Hg or more; circles indicate negative responses, whereas dashes signify a fall of 10 mm. Hg or more. Local anesthesia and curare immobilization were employed. A 4- to 10-volt, saw-tooth stimulus was delivered at frequencies of 30 to 240 cps for a duration of 10 to 60 seconds with a bipolar stimulating electrode. Blood pressures were recorded at the femoral artery with an electromanometer.

were obtained. After a period of further control blood pressure readings over an interval of 3 weeks to 15.5 months (average, 4.5 months) subsequent to the moderator nerve section, a cortical ablation was performed. A total of 28 cortical ablations were done in 11 dogs, which

survived such procedures for 2.5 to 20 months before hypothalamic lesions were made or the experiment was terminated. During this interval repeated blood pressure determinations were obtained. The extent of the cortical ablations was determined by gross and histologic studies. These cortical resections included four bilateral anterior cingulate gyrectomies, four bilateral ablations of the orbital cortex, two bilateral partial ablations of the motor cortex, three incomplete bilateral frontal lobectomies, and one bilateral ablation of the occipital cortex.

Fig.4.—Vasomotor responses obtained from the cingulate gyrus are illustrated above, as described for Figure 3, the results in the hypertensive dogs being represented in the upper drawing.

Nine of the 11 dogs in the cortical ablation series had red blood cell counts and hematocrit determinations. Satisfactory blood volume studies were obtained with the Evans blue technique six times in five of the dogs of this same group. These studies were carried out because of Schafer's report that dogs with neurogenic hypertension developed an increased blood volume and polycythemia.[13]

Multiple cortical areas were electrically stimulated in 10 normotensive and 7 hypertensive dogs under ether anesthesia or with the use of curare immobilization and local anesthesia. The

4-10 volt, saw-tooth type of stimulation was delivered at frequencies of 30 to 240 cps with a bipolar electrode for a duration fo 10 to 60 seconds. The stimulator used in these experiments delivered a saw-tooth type pulse whose total duration, including a 3% negative phase, was 1/240 second. The voltage and pulse duration were linear in the frequency ranges used in these experiments. Continuous blood pressure records were made with an electromanometer by femoral artery catheterization.

RESULTS

The neurogenic hypertension operation was performed upon 36 dogs. Ten of them died within one day to several weeks; 1 maintained a hypertension for only three months, and 1 of the survivors failed to become hypertensive.

Cortical Stimulation Studies.—A group of 10 normotensive dogs and 7 dogs with neurogenic hypertension had cortical stimulation studies. Two dogs in each group were stimulated under ether anesthesia, with essentially negative results except for moderate vasodepressor responses from the orbital cortex in the two hypertensive dogs. These minimal effects were likely related to the surgical depth of the anesthesia.

Cortical stimulation with local anesthesia and curare immobilization was performed 295 times in 8 normotensive and 5 hypertensive dogs. Only blood pressure changes greater than 10 mm. Hg were considered as positive results, and responses were not regarded as negative unless the stimulus was at least 10 seconds in duration. Most of the results (81% of the rises and 68% of the falls) exceeded 10 mm. Hg, most commonly being in the 20 to 30 mm. Hg range. Both pressor and depressor responses were obtained from each area of the cortex which yielded vasomotor responses. A given cortical site might reply with a pressor response on one occasion and a few moments later with a depressor response (Figs. 1 and 2). The orbital gyri, motor cortex, and cingulate gyri were found to give the most consistent vasomotor responses, but the temporal lobe was not as thoroughly explored (Figs. 3 and 4).

In the hypertensive group, of 5 dogs, there were 41 blood pressure rises, 32 falls, and 49 negative responses in 122 stimulations, whereas the normotensive group had a total of 173 stimulations, of which 82 gave rises greater than 10 mm. Hg, 24 resulted in a fall in blood pressure, and 67 yielded no significant change (Figs. 3 and 4). The character of the cardiovascular responses obtained in curarized preparations was essentially the same in normotensive and in hypertensive dogs.

Cortical Ablation Studies.—Eleven hypertensive dogs had a total of 28 cortical ablations, which included 4 bilateral anterior cingulate gyrectomies, 4 bilateral orbital cortex ablations, 2 bilateral partial ablations of the motor cortex, 3 incomplete bilateral frontal lobectomies, and 1 bilateral occipital cortex ablation. Of this group, eight dogs developed an immediate and persistent type of hypertension after section of the moderator nerves. In two dogs the hypertension was not well established until after the first postoperative month, and in one dog (Dog 363) a vacillating type of hypertension was created.

(*a*) Orbital Cortex Ablations: Bilateral orbital cortex ablations were performed in four dogs with neurogenic hypertension (Figs. 5, 6, 7, and 8). In none of these experiments was a persistent fall in blood pressure obtained. One dog (Fig. 6) had a normal blood pressure when killed, 15 months after the last cortical ablation. This dog was the only one in this series to develop such a vacillating type of hypertension. Because of the variability of the hypertension prior to the cortical ablations, it is

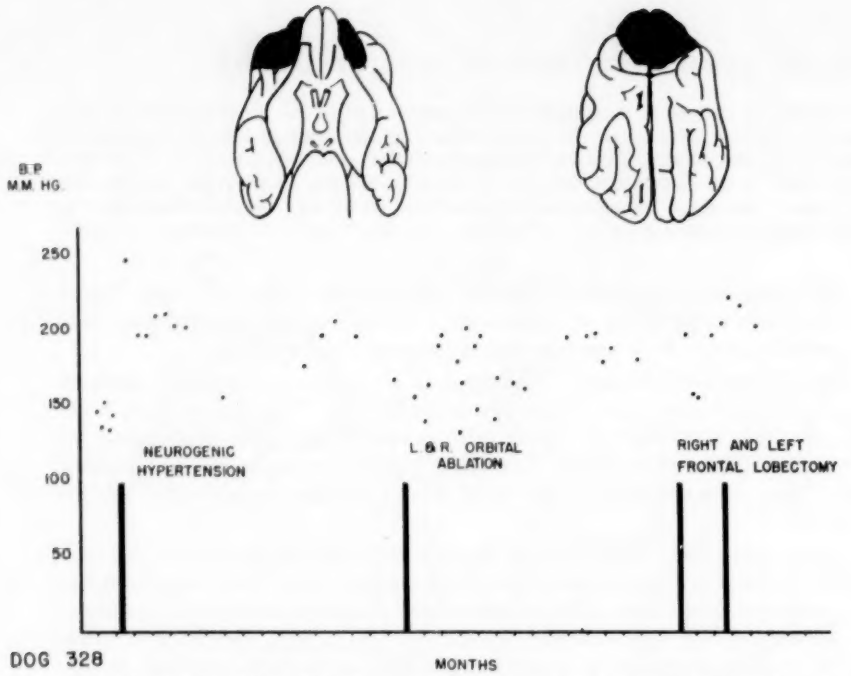
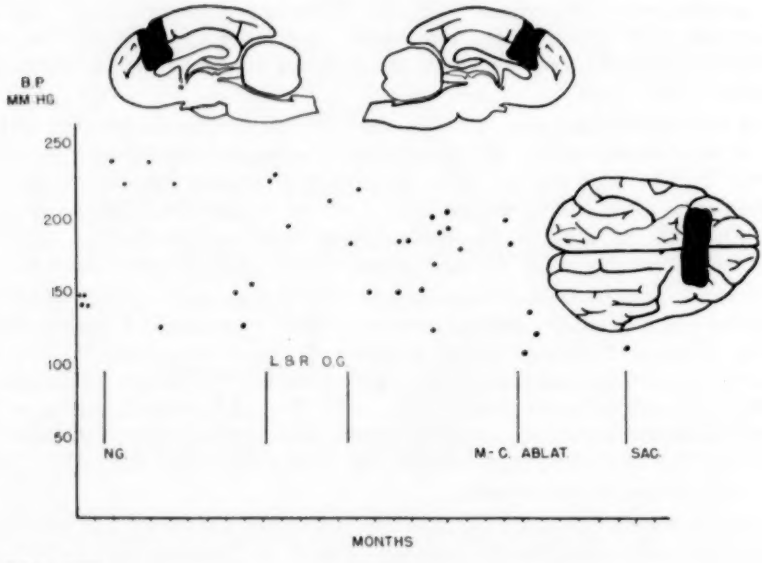
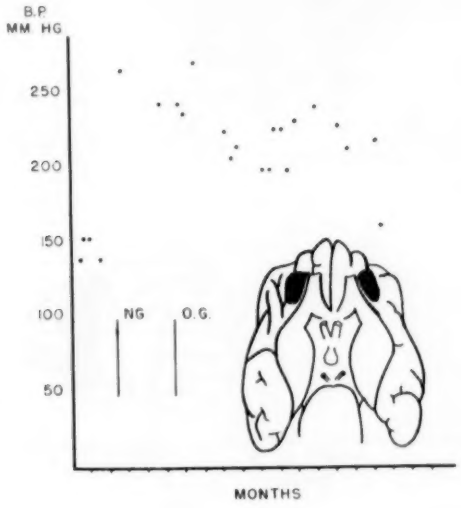


Fig. 5 (Dog 328).—This dog maintained a moderately severe hypertension for three years, which was not significantly altered by bilateral orbital gyrectomy and frontal lobectomy.



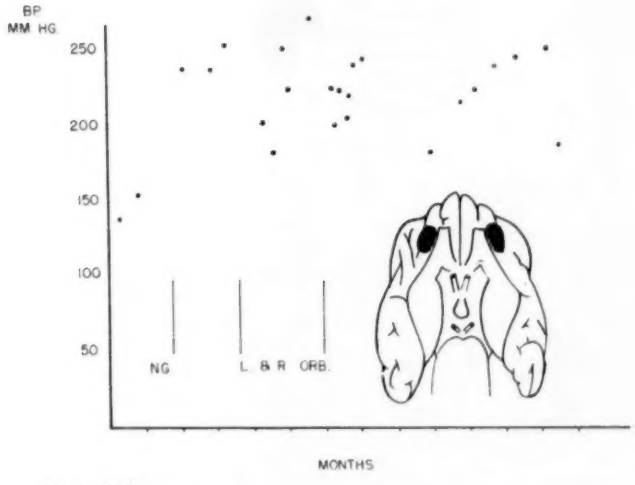
DOG 363

Fig. 6 (Dog 363).—This dog developed a vacillating type of hypertension, so that, even though the blood pressure was in the normal range at the time the animal was killed, this result could not definitely be attributed to the cortical excisions. It became impossible to enter the femoral artery percutaneously, so that the only blood pressure recorded in the last four months was obtained when the dog was killed. The bilateral orbital gyrectomy is not illustrated, but the extent was comparable to the orbital gyrectomies in the other dogs of this group.



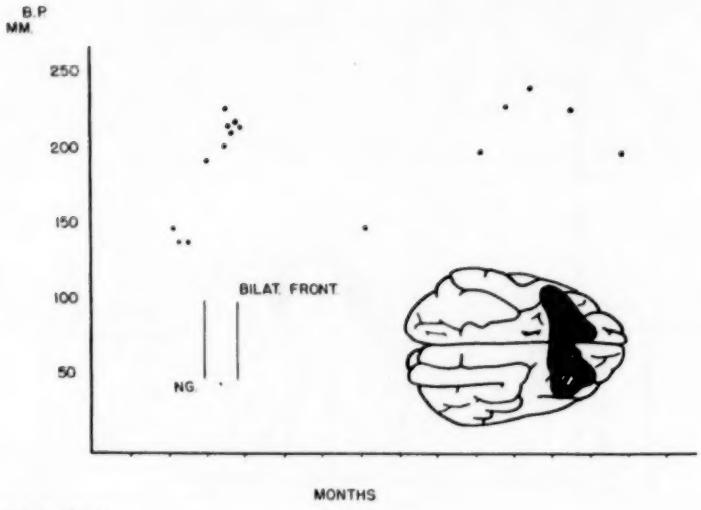
DOG 373

Fig. 7 (Dog 373).—Hypertension persisted essentially unaltered in this dog for 11 months after a bilateral orbital gyrectomy.



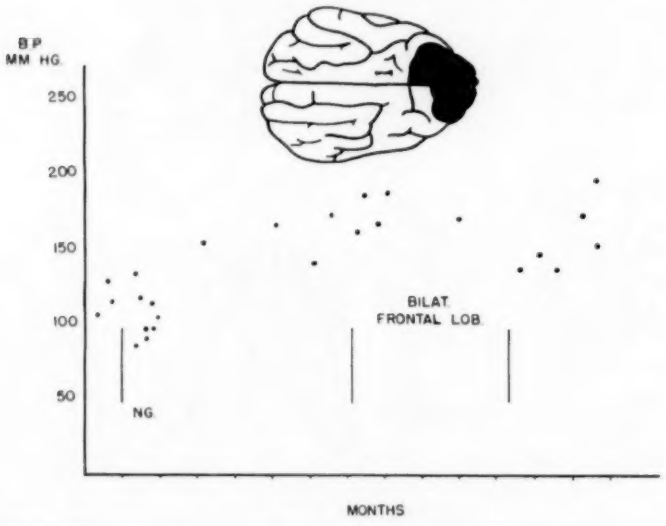
DOG 380

Fig. 8 (Dog 380).—A bilateral orbital gyrectomy failed to cure neurogenic hypertension in this dog.



DOG 386

Fig. 9 (Dog 386).—In this dog a limited frontal cortex excision did not abolish the hypertension.



DOG 388

Fig. 10 (Dog 388).—An incomplete bilateral frontal lobectomy did not significantly alter this dog's hypertension.

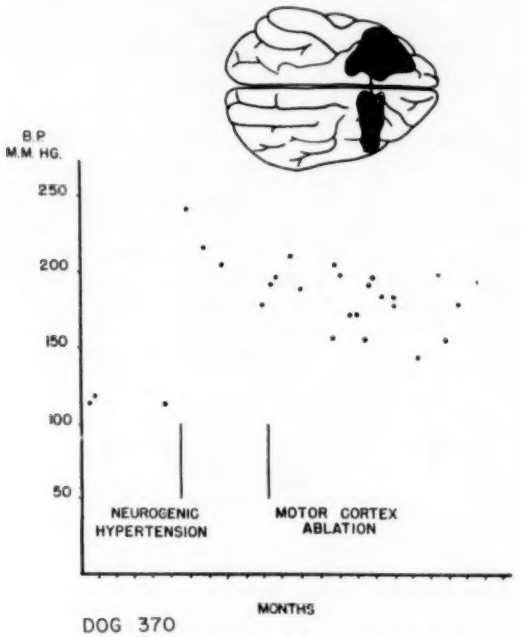


Fig. 11 (Dog 370).—This partial motor cortex ablation resulted in no essential change in the hypertension over a 12-month observation period.

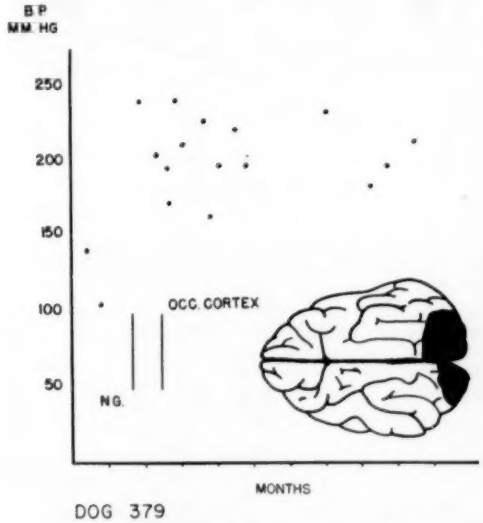
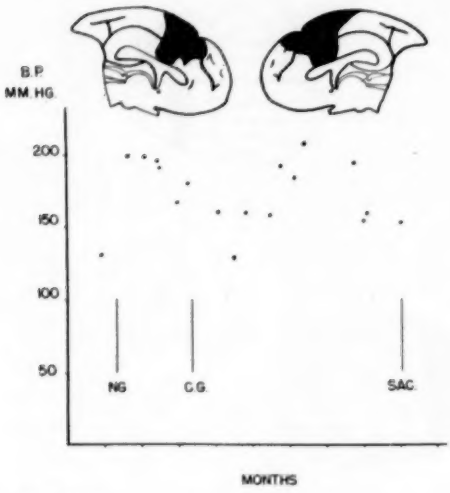
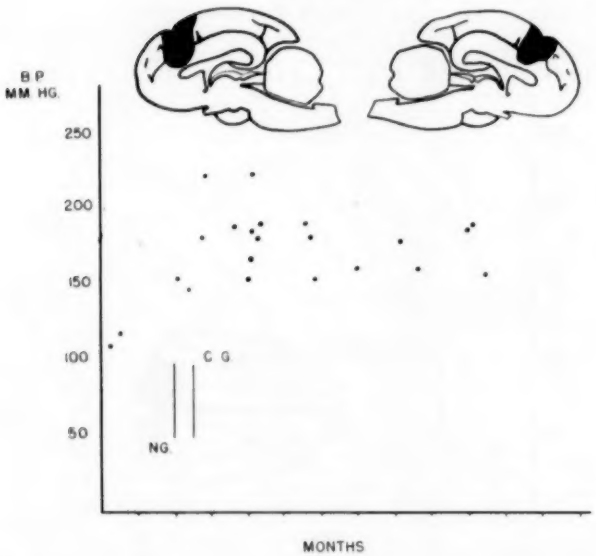


Fig. 12 (Dog 379).—An occipital cortex ablation, performed as a control procedure, failed to lower the blood pressure of this dog over a 7-month postoperative period.



DOG 378

Fig. 13 (Dog 378).—A portion of the anterior cingulate gyrus was resected in this dog together with the medial extent of the motor cortex. Although the blood pressure showed a transient fall, it soon returned to hypertensive levels.



DOG 383

Fig. 14 (Dog 383).—A resection of the medial motor cortex and a limited portion of the cingulate gyri failed to alter the hypertension in this dog.

impossible to state that the subsequent cortical ablations were responsible for the low blood pressures which were recorded after the bilateral resection of the motor and cingulate gyri.

(*b*) Frontal Lobectomy: The three bilateral frontal lobectomies performed were actually fractional frontal cortex resections in the prefrontal area (Figs. 5, 9, and 10). None of these procedures was followed by a persistent significant fall in the hypertension.

(*c*) Motor Cortex Ablations: The medial extent of the motor cortex was not resected in one of the two dogs making up this group.

Dog 363 (Fig 6). In this dog the motor cortex ablation was done concomitantly with a bilateral ablation of the anterior cingulate gyrus. As previously mentioned, this dog's preoperative vacillating hypertension was so marked that the eventual low blood pressures recorded could not be attributed to the cortical extirpation.

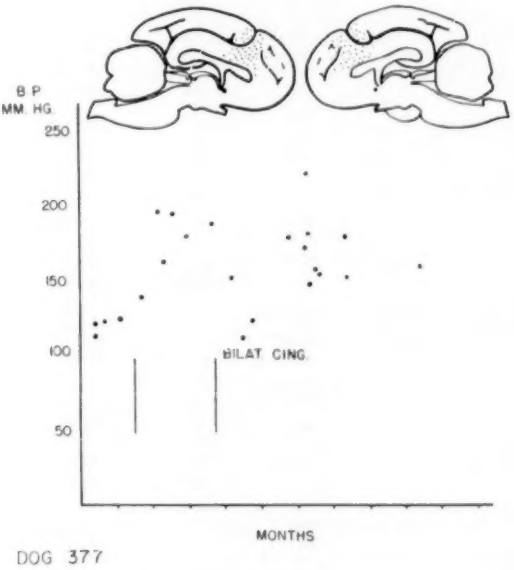


Fig. 15 (Dog 377).—A bilateral resection of the anterior portion of the cingulate gyri and the medial motor cortex in this dog had no significant effect upon its hypertension.

Dog 370 (Fig. 11). This dog was observed for 12.5 months after an incomplete ablation of the motor cortex. No significant alteration in the hypertension was noted.

(*d*) Occipital Cortex Ablation: The occipital cortex was ablated as a control procedure because it represented a region from which cardiovascular effects could not be obtained with facility, in contrast to the motor, orbital, and cingulate areas.

Dog 379 (Fig. 12). This dog remained hypertensive for the duration of the seven-month postoperative observation period.

(*e*) Cingulate Cortex Ablations: Four bilateral partial cingulate gyrectomies were performed.

Dog 363 (Fig. 6). This is the same animal as that previously discussed whose final normal blood pressure was not attributed to the multiple cortical ablations because a number of normal

readings were obtained prior to the performance of the cortical ablations. The remaining dogs in this group failed to evidence a persistent fall in their hypertension (Figs. 13, 14, 15).

Blood Studies.—Various blood studies were carried out in 9 of the 11 dogs with neurogenic hypertension in the cortical ablation series. The results of these studies, which were all performed subsequent to the cortical ablations and prior to the making of other lesions, are given in the accompanying Table.

Blood Studies After Cortical Ablations in Dogs with Neurogenic Hypertension

Dog	Red Blood Cell Count, Millions	Hematocrit, %	Blood Volume *		
328	7.73	65.0	....	.....	.....
377	4.82	43.0	Wt.	7.7 kg.	7.7 kg.
	5.25	43.9	PV	472 cc.	488 cc.
	....	39.0	BV	768 cc.	800 cc.
	....	38.5	Hgb.	38.5 %	39.0 %
378	5.28	47.0	Wt.	8.0 kg.	.....
	4.22	43.5	PV	430 cc.	.....
	5.38	48.0	BV	827 cc.	.....
	....	42.0	Hgb.	48 %	.....
365	6.96	55.5	....	.....	.....
383	....	52.0	Wt.	8.5 kg.	.....
	....	....	PV	489 cc.	.....
	....	....	BV	875 cc.	.....
	....	....	Hm.	52.0 %	.....
373	7.41	69.0	Wt.	11.0 kg.	.....
	9.62	71.0	PV	422 cc.	.....
	7.49	66.0	BV	1,360 cc.	.....
	....	62.0	Hgb.	69.0 %	.....
380	6.42	52.0	....	.....	.....
	7.48	53.5	....	.....	.....
	6.80	54.0	....	.....	.....
	....	55.5	....	.....	.....
	....	55.0	....	.....	.....
	....	58.0	....	.....	.....
379	8.40	60.0	Wt.	7.6 kg.	.....
	....	....	PV	284 cc.	.....
	....	....	BV	932 cc.	.....
	....	....	Hgb.	8.40 %	.....
370	6.37	68.0	....	.....	.....
	6.76	69.0	....	.....	.....
	....	55.5	....	.....	.....
	....	58.0	....	.....	.....

* PV indicates plasma volume; BV, blood volume; Hgb, hemoglobin, in percentages.

COMMENT

Despite the fact that cortical stimulation studies indicated that marked vasopressor and vasodepressor responses could be elicited by electrical stimulation of the posterior orbital, motor, and anterior cingulate cortices of dogs with neurogenic hypertension, the ablation of two or more of these areas failed to alter significantly their hypertension. Furthermore, ether anesthesia abolished vasopressor cortical responses without lowering the neurogenic hypertension in dogs to a significant degree. It was concluded that "autonomic zones" of the cerebral cortex may exert an important transient modulating influence upon medullary cardiovascular centers in the dog but that these centers were not affected chronically by such cortical ablations.

Although results of cortical ablations in dogs with neurogenic hypertension cannot be directly related to the treatment of essential hypertension in man, there are certain considerations which would seem to indicate that the excision of autonomic zones of the cerebral cortex in man may not prove to be an effective or a practical method for the treatment of essential hypertension.

Firstly, each area of the cortex concerned with vasomotor responses yields both vasopressor and vasodepressor responses to stimulation, and these points of opposite signs are so admixed spatially as to render their separate excision a surgical impossibility. Indeed, it was not uncommon to observe a reversal of response on successive stimulation of a given point. Secondly, such cortical areas are multiple in number and widespread in distribution, so that their complete ablation would entail several operations and would likely result in serious neurologic deficits.

SUMMARY

The results of 28 cortical ablations in 11 dogs with chronic neurogenic hypertension created by moderator nerve section are presented.

Excision of one or more cortical areas concerned with autonomic functions had no demonstrable effect upon this type of hypertension.

Neurogenic hypertension induced by sectioning the moderator nerves results in a hyperactivity of medullary cardiovascular centers. This activity is not chronically altered by multiple resections of "autonomic zones" of the cerebral cortex.

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CLINICAL IMPLICATIONS OF RECENT STUDIES ON CEREBRAL CIRCULATION OF MAN

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THE NITROUS oxide method, introduced by Kety and Schmidt,[1] has made it possible for the first time to measure quantitatively the cerebral blood flow (CBF) in the intact human being. Utilizing such data with the simultaneously measured blood pressure and oxygen contents of arterial and jugular blood, it is possible to calculate the resistance offered to blood passing through the cerebral vessels (CVR) and the oxygen consumption ($CMRO_2$) of the brain. While much of such information thus far is purely of physiological interest, many considerations of clinical importance have emerged.

EFFECTS OF ARTERIOSCLEROSIS AND HYPERTENSION ON THE CEREBRAL CIRCULATION

Arteriosclerosis in the absence of hypertension does not materially reduce the over-all blood flow or oxygen consumption of the brain (Table 1).[2] Twenty-three patients, of an average age of 68, were studied. They all exhibited clinical evidence of the presence of systemic arteriosclerosis, such as historical or electrocardiographic evidence of coronary artery disease, aortic or carotid artery calcification on x-rays, peripheral vascular ischemia, retinal arteriosclerosis, and, in three patients of the group, a history of a previous cerebral thrombosis. It may be presumed from this evidence of systemic arteriosclerosis that some degree of cerebral arteriosclerosis existed in each case studied. While the average cerebral blood flow (CBF) of this group (46 cc./100 gm./min.) was lower than normal, the difference lacked statistical significance. Similarly, average values for $CMRO_2$ and CVR in this group did not vary significantly from such values obtained for normal young persons.

Hypertension unaccompanied by clinical evidence of arteriosclerosis does not alter the CBF or $CMRO_2$ from normal although a marked increase in cerebrovascular resistance does occur (Table 2). The increase in CVR in hypertension is evidence that the cerebral vessels participate in the generalized increase of vascular resistance which is the outstanding characteristic of essential hypertension.

However, when clinically evident arteriosclerosis and hypertension coexist, significant lowering of the CBF and $CMRO_2$ do occur (Table 3). The cerebral blood flow is reduced on the average about 30%, and the $CMRO_2$, 25%. It can thus be

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concluded that where hypertension and arteriosclerosis coexist a severer and more diffuse degree of arteriosclerosis, particularly of the arteriolar type, results than when arteriosclerosis occurs without hypertension.

The relationship of the above findings to the clinically observed mental changes often associated with cerebrovascular disease are of great interest. In the first place,

TABLE 1.—*Cerebral Circulatory Data on Arteriosclerotic Normotensive Patients*

Subject	Age	MABP, Mm. Hg	CBF, Cc./ 100 Gm./ Min.	CVR, Mm. Hg/ Cc./100 Gm./ Min.	$CMRO_2$, Cc./100 Gm./ Min.
M. D.	59	100	48	2.0	3.3
S. A.	64	90	29	3.2	1.5
H. S.	75	100	38	2.6	3.0
J. P.	70	77	98	0.8	6.4
E. G.	56	98	54	1.7	3.9
B. D.	68	95	45	1.8	2.8
W. H.	55	100	41	2.2	2.8
E. L.	66	91	80	1.1	3.1
E. G.	55	86	33	2.4	1.0
M. S.	62	100	36	2.6	2.2
W. F.	73	107	48	2.1	3.2
M. So.	65	102	40	2.4	2.4
H. K.	65	93	54	1.6	2.9
F. P.	75	88	51	1.6	2.7
B. B.	75	90	32	2.6	2.0
S. K.	58	72	51	1.3	3.5
J. L.	76	115	42	2.7	3.3
A. P.	80	98	42	2.3	2.3
C. Z.	86	105	37	2.7	1.0
J. S.	45	105	41	2.3	2.2
A. Di.	61	96	45	2.0	2.7
I. K.	69	87	40	2.1	2.1
T. B.	69	88	30	2.7	1.7
Mean	68	95	46	2.1	2.7
Normal mean	30	91	53	1.8	3.4

TABLE 2.—*Cerebral Circulatory Data on Hypertensive Patients Without Clinical Arteriosclerosis*

Subject	Age	MABP, Mm. Hg	CBF, Cc./ 100 Gm./ Min.	CVR, Mm. Hg/ Cc./100 Gm./ Min.	$CMRO_2$, Cc./100 Gm./ Min.
B. B.	38	133	50	2.5	3.1
G. B.	38	154	60	2.4	3.7
C. H.	46	160	47	3.2	3.3
S. P.	39	116	55	1.9	2.8
D. B.	45	132	67	1.9	3.7
B. S.	56	121	31	3.5	1.9
Mean	44	136*	52	2.6*	3.1
Normal mean	30	91	53	1.8	3.4

* Statistical difference $P < 0.01$.

it is clear that over-all changes in cerebral circulation and oxygen consumption cannot be correlated with the occurrence of mental symptoms, since all patients in the above groups, even where the cerebral circulation was impaired, did not exhibit mental aberrations. A previous report [3] suggesting such a correlation did so on the basis of comparing results of cerebral circulatory studies in senile psychotics

with results obtained in a series of normal young persons. It was recognized by the authors that the latter series did not offer a suitable comparison, but it was the only control group available at the time of their report. When the cerebral circulatory data of the senile psychotic patients are compared with patients of the same age and with clinically similar degrees of hypertensive vascular disease but without psychoses (Table 4), no real differences in cerebral circulation are noted. It can only be concluded that when mental disease is associated with arteriosclerotic or hypertensive vascular disease the particular changes responsible for the mental changes are so focal as not to affect the over-all cerebral circulatory values, or else some portions of the cerebral vasculature are so seriously affected as to be excluded

TABLE 3.—*Cerebral Circulatory Data on Hypertensive and Arteriosclerotic Patients Without Clincal Cerebrovascular Diseases*

Subject	Age	MABP, Mm. Hg	CBF, Cc./100 Gm./Min.	CVR, Mm. Hg/Cc./100 Gm./Min.	$CMRO_2$, Cc./100 Gm./Min.
M. S.	68	120	33	3.5	2.4
S. F.	64	132	33	3.9	2.6
J. L.	62	156	41	4.7	2.7
A. W.	62	125	44	2.6	3.7
E. S.	66	138	30	3.3	1.6
I. B.	41	160	42	3.6	1.6
Mean	61	139*	39*	3.4*	2.4*
Normal mean	30	91	53	1.8	3.4

* Statistical difference $P < 0.01$.

TABLE 4.—*Comparison of Mean Values of Cerebral Circulatory Functions Obtained by Authors for Hypertensive Arteriosclerotic Patients Without Psychosis and Similar Group Reported[3] With Psychosis*

	MABP, Mm. Hg	CBF, Cc./100 Gm./Min.	$CMRO_2$, Cc./100 Gm./Min.	CVR, Mm. Hg/Cc./100 Gm./Min.
Kety and others	136	42	2.8	3.3
Shenkin and Novack	139	39	2.4	3.4

from the general cerebral circulation, and therefore do not influence the values obtained for the latter.

A further study [4] to determine the reactivity of the cerebral vessels has certain therapeutic implications in patients with cerebrovascular disease. Kety and Schmidt [5] have demonstrated that the human cerebral vessels are sensitive to alterations of the partial pressure of carbon dioxide in the blood. Inhalations of 5% CO_2, by raising the partial pressure of carbon dioxide in the blood, dilate the cerebral vessels, thereby reducing the CVR and increasing the CBF on the average by 40% in normal young subjects. The cerebral vessels appear to be specifically affected, the systemic vessels remaining relatively unchanged. It therefore would appear that the use of CO_2 inhalations would offer a means of testing the ability of the cerebral vessels to alter their diameter in various disease states. The group of patients with arteriosclerotic vascular disease without concomitant hypertension had little, if any, ability to dilate their cerebral vessels when given CO_2 inhalations (Table 5). The slight

rise in CBF that did occur was the result of a slight increase in mean arterial blood pressure (MABP) and a slight decrease in CVR, both the latter changes not being of statistical significance in themselves. From this it may be inferred that the vessels have become quite rigid, or else were already maximally dilated as a means of offsetting the arteriosclerotic narrowing. The further inference is that it is not to be

TABLE 5.—*Effects of Inhalation of 5% CO_2 on Cerebral Circulatory Functions of Aged Normotensive Arteriosclerotic Persons*

Subject	Age	CBF, Cc./100 Gm./Min.		CVR, Mm. Hg/Cc./100 Gm./Min.		$CMRO_2$, Cc./100 Gm./Min.		MABP, Mm. Hg	
		I	II	I	II	I	II	I	II
M. D.	59	48	46	2.0	2.3	3.3	3.6	100	110
S. A.	64	29	39	3.2	2.4	1.5	1.7	99	100
H. S.	75	38	39	2.6	2.8	3.0	1.9	100	113
J. P.	70	98	99	0.8	0.8	6.4	3.9	77	79
E. G.	56	54	63	1.7	1.6	3.9	3.9	98	111
B. D.	68	45	50	1.8	1.6	2.8	2.5	95	92
E. Gi.	56	33	42	2.4	1.8	1.0	1.8	86	79
M. S.	62	36	33	2.6	3.0	2.2	1.5	100	108
S. K.	58	51	68	1.3	1.1	3.5	3.2	72	76
J. L.	76	42	66	2.7	1.7	3.3	3.6	115	115
Mean	64	47	55*	2.1	1.9	3.1	2.7	94	98

* Indicates statistical significance $P < 0.01$.

TABLE 6.—*Effects of Inhalation of 5% CO_2 on Cerebral Circulatory Functions of Hypertensive Arteriosclerotic Persons*

Subject	Age	CBF, Cc./100 Gm./Min.		CVR, Mm. Hg/Cc./100 Gm./Min.		$CMRO_2$, Cc./100 Gm./Min.		MABP, Mm. Hg	
		I	II	I	II	I	II	I	II
M. S.	68	33	39	3.5	3.1	2.4	2.6	120	125
S. F.	64	33	46	3.9	2.6	2.6	1.6	132	130
E. S.	66	51	32	2.5	4.1	2.6	1.9	141	145
S. L.	56	41	94	3.0	1.4	2.8	5.2	123	133
S. S.	45	23	24	6.3	6.0	2.5	...	140	150
C. K.	50	29	48	4.9	3.6	2.6	2.6	143	172
S. G.	51	34	60	3.8	2.1	2.1	2.1	117	135
D. K.	60	33	46	3.4	2.0	2.6	2.2	120	100
J. L.	62	41	50	3.7	3.2	2.7	2.6	156	169
M. W.	48	44	54	2.6	2.1	3.7	3.1	125	128
Mean	57	36	49*	3.7	3.0*	2.6	2.7	132	139*

* Indicates statistical significance $P < 0.01$.

expected that inhalations of CO_2 or any other vasodilating agent would be of any value in combating the symptoms due to cerebral arteriosclerosis, unless there is evidence of accompanying vasospasm reducing the CBF. At the present time this could only be determined by actual cerebral circulatory studies during the acute phase of the cerebral accident.

However, when CO_2 inhalations were administered to arteriosclerotic patients who were also hypertensive, a significant reduction of CVR did result, amounting on the average to 19% (Table 6). The reduction in CVR is indicative of a widening of the vascular bed, since there was no alternation of the viscosity of the blood as a

result of the CO_2 inhalations. It is clear, then, that a severe degree of arteriosclerosis per se does not abolish cerebral vascular reactivity. Rather, it appears that in the absence of hypertensive constriction, the cerebral vessels are already nearly maximally dilated as a mechanism compensatory to the development of arteriosclerosis. This conclusion is reinforced by the further demonstration that arteriosclerotic cerebral vessels can be constricted by hyperventilating the patients and reducing their blood CO_2 content.[6] Totally rigid vessels would hardly react in this manner.

A second conclusion to be drawn from the finding that increasing the CO_2 content of the blood can in a measure dilate the cerebral vessels of hypertensive arteriosclerotic patients is that the vasodilating measures can be applied hopefully in an effort to produce improvement in the cerebral circulation. An inspection of Table 6 further indicates that some subjects in this group far exceed the average reduction of 19% in the CVR when the CO_2 content of the blood is increased. It is permissible to assume that these persons would be particularly susceptible to the benefits of vasodilating efforts.

EFFECTS OF DRUGS ON THE CEREBRAL CIRCULATION

The xanthines have long been advocated as efficient cerebral vasodilator agents. The availability of a direct method for measuring the cerebral circulation in humans has proved this conclusion to be false. Caffeine and sodium benzoate given intramuscularly increased the CVR and reduced the cerebral blood flow by 15%.[7] Aminophylline similarly reduced the cerebral blood flow of normal subjects [8] and of patients in cardiac decompensation.[9]

Nicotinic acid given intravenously has frequently been used as a cerebral circulatory stimulant. Nevertheless, when its effects on the cerebral circulation were quantitatively measured, it was found that nicotinic acid does dilate the vessels of the external carotid complex but is ineffective in dilating the cerebral vessels.[10]

Newer vasodilator drugs, such as benzazoline (Priscoline), have been advocated for the treatment of cerebrovascular disease. Again, when the effects were quantitatively measured, this drug proved to have little effect, and this effect was in the direction of constricting the cerebral vessels.[11]

Papaverine, on the other hand, does seem to have a specific effect on the cerebral vessels when given in large doses, particularly by intravenous administration.[7] When 0.2 gm. is given intravenously, a 13% increase in CBF will result despite a decrease in systemic arterial pressure.

It would appear then that CO_2 inhalations given in 5 to 7% concentration remains the most effective cerebral vasodilator available. In health a 40% increase in cerebral blood flow may be expected to result from such treatment. However, it should be pointed out that when the patient is in cardiac failure or has a poor cardiac reserve, CO_2 inhalations may further embarrass the general circulation and produce a reduction of the cerebral blood flow.* It is frequently the case that in patients for whom it would be desirable to increase the cerebral blood flow, as after a cerebral thrombosis, the cardiac reserve is reduced by the same vascular disease process. It has been found that the effects of CO_2 inhalations on the general circulation can be roughly predicted by measuring the immediate effects of the CO_2 on the brachial venous pressure. When cardiac reserve is good, the brachial venous pressure will

* Novack, P., and Shenkin, H. A.: Unpublished observations.

remain unchanged or will decrease with CO_2 inhalations. When the heart is decompensated, or even when cardiac reserve is markedly reduced, the brachial venous pressure will rise after the onset of CO_2 inhalation.†

In summary, then, it appears that there are very few agents with any real ability to dilate cerebral vessels and increase the cerebral blood flow. Raising the carbon dioxide content of the blood is the most effective method, and papaverine in adequate dosage has a limited ability to secure cerebral vasodilatation without drastically reducing the systemic blood pressure. Histamine given intravenously will unquestionably dilate cerebral vessels, but this is a nonspecific effect and the accompanying peripheral vasodilatation so reduces the head of pressure that the net result is a decrease in cerebral blood flow.[7]

SYMPATHETIC INNERVATION OF THE CEREBRAL VESSELS

The sympathetic innervation of the cerebral vessels has been repeatedly demonstrated in the experimental laboratory, but the importance of its role in the regulation of the human cerebral circulation is disputed. Recent reports have claimed a remarkable efficacy for the blocking of sympathetic fibers to the cerebral vessels in

TABLE 7.—*Effects of Bilateral Stellectomy upon Cerebral Circulatory Functions*

Subject	Age	CBF, Cc./100 Gm./Min.		CVR, Mm. Hg/Cc./100 Gm./Min.		$CMRO_2$, Cc./100 Gm./Min.		MABP, Mm. Hg	
		I	II	I	II	I	II	I	II
E. S.	45	51	42	2.5	2.6	2.6	2.1	141	122
M. B.	53	44	56	3.9	2.6	2.5	2.6	180	156
J. M.	71	44	50	2.7	2.9	2.5	3.6	122	109
P. C.	52	29	59	5.9	2.8	1.9	4.1	179	170

an effort to increase the cerebral circulation following cerebral thrombosis or embolism. The method generally recommended is the infiltration of the stellate ganglion with procaine. However, direct measurements of the cerebral blood flow with the nitrous oxide technique before and after stellate ganglion block failed to reveal any appreciable effect.[12] On the other hand patients studied before and after bilateral stellate ganglionectomy have been demonstrated to exhibit a definite measure of cerebrovascular relaxation.[13] A series of four cases recently studied adds further confirmation of the data originally reported in 1951 (Table 7). Analysis of all data on the effects of stellate ganglionectomy on the cerebral circulation reveals that improvement in cerebral circulation was greatest in those patients with the initially slowest cerebral blood flows and the initially highest cerebrovascular resistances. Such studies suggest that, although the sympathetic nervous system usually makes a minimal contribution to the maintenance of cerebrovascular tone, it does influence the cerebral vessels and its effect may become very significant in certain pathological states.

It would appear that one might predict the efficacy of performing stellate ganglionectomy preoperatively. If it can be established that the cerebral circulation is definitely slowed owing to an increased CVR, then it may be anticipated that sympathectomy might be effective in relaxing the cerebrovascular resistance. When

† Novack, P., and Shenkin, H. A.: Unpublished observations.

this concept is applied to the above-cited effects of arteriosclerosis upon the cerebral circulation, it is to be expected that stellectomy would be less apt to be beneficial in nonhypertensive arteriosclerotic patients, in whom the cerebral blood flow is not materially reduced and the cerebrovascular resistance is not materially increased. Moreover, it was also demonstrated by the studies on the effects of 5% CO_2 inhalations that in such instances the vessels are already maximally relaxed, so that neither sympathectomy nor any other procedure directed toward obtaining vasodilatation could accomplish much in cerebral arteriosclerosis per se. On the other hand, sympathectomy for the treatment of cerebrovascular disease would seem to be of greatest possible value in patients with hypertension and arteriosclerosis, in which there are a reduced CBF and an increased CVR, the prerequisites for stellectomy to be effective in increasing the cerebral circulation.

It is undoubtedly the previous lack of criteria for the proper selection of patients likely to benefit from stellate ganglion block or stellectomy that has led to the

TABLE 8.—*Effects of Inhalations of 5% CO_2 on Cerebral Circulatory Functions and Cerebrospinal Fluid Pressure in Normal Young Persons*

	CBF, Cc./100 Gm./Min.			CSFP, Mm. H_2O			CVR, Mm. Hg/Cc./100 Gm./Min.			MABP, Mm. Hg		
Subjects	I	II	Δ %	I	II	Δ %	I	II	Δ %	I	II	Δ %
S. W.	77	89	+16	230	250	+ 9	1.0	0.9	—10	84	90	+ 7
D. O.	57	92	+61	210	480	+129	1.3	0.9	—31	83	90	+ 8
S. D.	78	102	+31	210	280	+33	1.1	0.9	—18	91	104	+14
E. G.	54	61	+13	226	230	+ 2	1.7	1.4	—18	100	94	— 6
S. K.	74	77	+ 4	260	370	+42	1.1	1.1	0	95	97	+ 2
A. H.	52	64	+23	164	220	+34	2.0	1.7	—15	111	111	0
R. S.	38	80	+110	225	280	+24	2.5	1.3	—48	100	105	+ 5
D. M.	54	78	+44	240	290	+21	1.3	0.9	—31	79	82	+ 4
M. H.	22	81	+268	210	400	+90	3.9	1.0	—74	91	92	+ 1
S. G.	35	48	+37	70	100	+43	2.1	1.6	—24	81	85	+ 5
F. B.	47	64	+36	105	175	+67	1.5	1.2	—20	70	100	+28
G. C.	47	57	+15	275	350	+27	1.8	1.7	— 6	90	105	+ 6
Mean	53	74*	+55	202	285*	+43	1.8	1.2*	—24.6	91	96	+ 6.1

* Indicates statistical significance $P < 0.01$.

divergence of opinions on the effectiveness of these procedures. Although our data provide indications likely to result in better selection of cases for these procedures, it still must be admitted that the application of such clinical criteria to the individual instance cannot always be correct. Direct measurements of the cerebral circulation would offer the best means of selection. Unfortunately, the nitrous oxide method at present is not applicable as a practical clinical test in seriously ill patients.

RELATIONSHIP OF THE CEREBRAL CIRCULATION AND CEREBROSPINAL FLUID PRESSURE

It had been noted in studying the effects of alterations of the CO_2 content of the blood on the cerebral blood flow that changes occurred in the cerebrospinal fluid pressure (CSFP). Indeed, in patients with relatively normal cerebral vasculature the changes in cerebrospinal pressure correlated well with changes in CBF.[14] Table 8 demonstrates the parallel increase in CBF and CSFP resulting from increasing the CO_2 content of the blood by inhalations of CO_2. Similarly, hyperventilation caused a parallel decrease in CBF and CSFP as a result of decreasing the CO_2 content of the blood.[14] Ryder and his co-workers [15] had reached similar conclusions

from careful measurements of the CSFP and arterial pressures, using drugs whose effects on the cerebral blood flow could be estimated. They concluded that changes in cerebral blood flow always induce changes in the CSFP in the same direction.

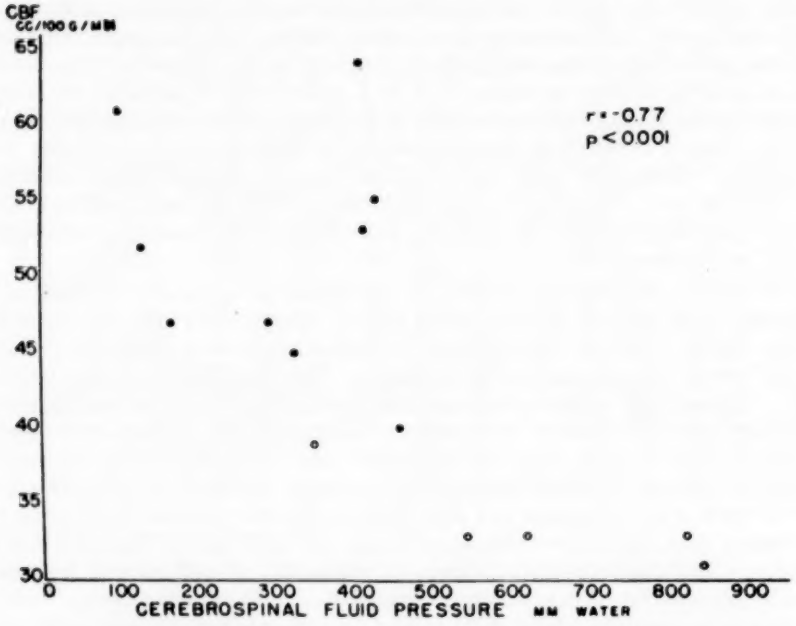
This important physiological relationship between alterations in the CSFP and the CBF has led to a better understanding of the syndrome of cerebral hypotension not infrequently encountered in patients after operation for relief from a subdural hematoma or an internal hydrocephalus.[16] Of three patients in whom this syndrome was recognized, a marked reduction of CBF was noted in each. This reduction of CBF could hardly result from the reduced CSFP, since the CSFP is an expression of a factor offering resistance to the flow of blood in the cerebral vessels and a primary decrease in CSFP should tend to increase the CBF. The correct interpretation undoubtedly, then, is that the reduced CBF in these patients contributes to the reduction of CSFP, rather than vice versa. Further, it is reasonable to believe that the production of cerebrospinal fluid is curtailed by the reduced cerebral circulation, and this further contributes to, if it is not a principal source of, the intracranial hypotension. These observations would suggest that reasonable therapy of the intracranial hypotensive syndrome would be directed toward increasing the cerebral circulation. The most powerful selective cerebrovascular dilator available is carbon dioxide, and in one instance in the above series of cases in which it was tried, it did prove effective in increasing the CBF and also tended to restore the CSFP to a normal level.

In general, reduced CSFP noted on routine lumbar punctures has been disregarded. Awareness of the relationship between alterations in CBF and those in CSFP may very well give new diagnostic importance to an observation of a reduced cerebrospinal fluid pressure and aid in therapy. Low cerebrospinal fluid pressures are not infrequently encountered in patients with clouded states of consciousness associated with hypertensive, arteriosclerotic cerebrovascular disease and its complications, as well as in toxic encephalopathies resulting from uremia and severe systemic infections. It is now reasonable to assume that the low CSFP is a reflection of relatively acute reductions in CBF. Therapy, therefore, should be directed to increasing the CBF; and, indeed, in our hands, gratifying results have been noted with regard to improvement in the state of consciousness in such patients from use of CO_2 inhalations.

Persistent headache following lumbar puncture and spinal analgesia had been consistently demonstrated to be associated with a low CSFP. This differs from the above-discussed instances of low CSFP so far as it is the result of loss of cerebrospinal fluid, and not the result of a primary disturbance of the cerebral circulation. Nevertheless, taking advantage of the known effect that an increase of the cerebral circulation increases the CSFP, we have used CO_2 inhalations in treatment of such headaches, and the results have been extremely gratifying, clinically. While we have not been able to demonstrate a reduced CBF in spinal drainage headache produced acutely by withdrawing 30 to 50 cc. of cerebrospinal fluid, increasing the CBF by CO_2 inhalation, with a concomitant increase of CSFP, was helpful in relieving such headache, experimentally produced.[17] Possibly the stimulation of the CBF also increases spinal fluid production and replacement.

Increased cerebrospinal fluid pressure increases the cerebrovascular resistance, as would be expected, since the capillaries of the brain, being freely collapsible, transmit any external pressure in opposition to the pressure head of the flowing

blood.[18] This increase in CVR represents the primary effect of high intracranial pressure. Were no compensatory mechanisms operating, this should result in a progressive restriction of the cerebral blood flow. That this does occur is evident from the good correlation noted between increasing intracranial pressure and restriction of cerebral blood flow (Chart). The relationship, however, is more complex than it appears to be in this single correlation. Careful analysis of the data reveals that up to a CSFP of 450 mm. of water the correlation is poor, indicating probably that in this range the compensatory rise in arterial pressure is sufficient to overcome the increased resistance, whereas this adjustment falls short in the regions of a higher CSFP. The patients who failed to compensate and exhbiited a reduction



THE RELATIONSHIP BETWEEN INTRACRANIAL PRESSURE AND CEREBRAL BLOOD FLOW

Open circles represent comatose patients.

of CBF below 40 cc./100 gm./min. were all comatose. The restriction of cerebral blood flow leads to progressive cerebral asphyxia, and this, in turn, leads to a rise in arterial blood pressure as a direct result of stimulation of the medullary vasomotor center. These findings in man complement Cushing's hypothesis derived from animal experiments, that medullary ischemia results from increased intracranial pressure and leads to a rise in blood pressure to a level somewhat above that in the cerebrospinal system.

Efforts to reduce increased intracranial pressure acutely in patients with brain tumor revealed that the CBF can be restored, at least temporarily, by intravenous administration of 150 cc. of 50% dextrose solution.[19] On the other hand, reduction

of increased intracranial pressure in man by ventricular drainage was ineffective in restoring the CBF to normal. It was concluded from this evidence that 50% dextrose solution could not have increased the CBF from the lowering of CSFP alone, since ventricular drainage which reduces intracranial pressure to a consistently lower level had no effect in reducing the CVR or in increasing the CBF. It is believed, rather, that dextrose causes a dilution of circulating blood, which, in turn, lowers blood viscosity and thus lowers the cerebrovascular resistance. The beneficial effects of hypertonic dextrose solution, since they are accompanied or caused by hemodilution, may be more apparent than real. The amount of oxygen delivered to the brain is the product of the CBF and arterial oxygen content. The dilution of the blood which results in the increased CBF also lowers the arterial oxygen content. As a consequence, we have found no change in the oxygen delivery to the brain after injection of hypertonic dextrose solution. Nevertheless, the increased CBF may well have beneficial effect by removing products of metabolism not dependent on hemoglobin transport.

SUMMARY

Measurements of the cerebral blood flow in man have been carried out in the past five years with the nitrous oxide method of Kety and Schmidt. Pertinent data concerning the effects of vascular disease, various drugs, and changes in intracranial pressure upon the cerebral circulation are reviewed. Recent information obtained from the studies concerning the sympathetic innervation of the cerebral vessels is also discussed.

255 S. 17th St. (3).

ABSTRACT OF DISCUSSION

DR. MICHAEL SCOTT, Philadelphia: I congratulate Dr. Shenkin on this fundamental work.

Some of Dr. Shenkin's observations suggest the limitation of blood-flow experiments in interpreting clinical results. For example, in discussing the absence of any difference in cerebral circulation in data obtained by the Kety-Schmidt method in a group of hypertensive senile psychotic patients and in a similar hypertensive age group who were not psychotic, Dr. Shenkin states: "It can only be concluded that when mental disease is associated with arteriosclerotic or hypertensive vascular disease, the particular changes responsible for the mental changes are so focal as not to affect the over-all cerebral circulatory value, or else some portions of the cerebral vasculature are so seriously affected as to be excluded from the general cerebral circulation, and therefore do not influence the value obtained for the latter."

Again, "Direct measurements of the cerebral blood flow with the nitrous oxide technique before and after stellate block failed to reveal any appreciable effect. On the other hand, patients studied before and after bilateral stellate ganglionectomy have been demonstrated to exhibit a definite measure of cerebrovascular relaxation."

Thus, apparently, a deficiency of this method is that, although it may give an over-all pattern of cerebral circulation, it gives no information as to local cerebrovascular function. Thus, a small local change in blood flow (for example, in the tiny lenticulostriate artery), although important clinically, might be completely neutralized by the total flow and cerebrovascular resistance of the entire brain, and the data therefore be called normal.

Although Dr. Shenkin states that some patients with cerebrovascular disease have been helped by bilateral stellate ganglionectomy, he warns that the applicability of criteria for selection, as determined by cerebral blood flow data, "cannot always be predicted"; further, "the nitrous oxide method at present is not applicable as a practical clinical test in seriously ill patients."

It appears at present that bilateral stellate ganglionectomy requires further investigation to establish its ultimate value.

Dr. Shenkin's blood flow determinations following stellate block are in agreement with the clinical impressions of many that the procedure is of debatable therapeutic value in cerebral thrombosis or embolism.

Again, I congratulate Dr. Shenkin and Dr. Novack. The importance of their work should not be minimized because of the limitations of the method. It will help in a better understanding of the physiology of the cerebral circulation and its clinical application.

DR. HENRY A. SHENKIN, Philadelphia: I wish to thank the discussers for their comments.

Dr. Rupp brought up a subject which I had no time to cover in the paper, that is, the question of the limitations of carbon dioxide inhalations. It must be admitted that when there is a poor cardiac reserve, as might often be the case in patients with cerebrovascular disease, there will be a probable drop in cerebral blood flow with CO_2 inhalations. The heart does not have the reserve to cope with the vasodilatation which occurs, particularly in the cerebral vessels. As a result, there will be a failure to increase the cardiac output, and, as a matter of fact, the head of pressure will so decline that the cerebral blood flow will be reduced.

This can be predicted by measuring the effect of carbon dioxide inhalations on the brachial venous pressure. Normally, there is no change in the branchial venous pressure. If there is a poor cardiac reserve, the brachial venous pressure will rise markedly.

Dr. Scott brought up the question of the limitations of the method. There are definite limitations, of course; but the emphasis should be in the other direction, I believe. Because we do not always understand the results obtained, and cannot always apply them from problem to problem or clinically, it does not mean the method has limited applicability. It may mean that our understanding is limited and that with further understanding of the variables concerned we shall be able to give a proper interpretation to the results obtained from cerebral blood flow studies.

The test is applicable clinically. It is a very simple test. I should not recommend it for persons who are in extremis or those who are very seriously ill (as they may be, for example, after a cerebrovascular accident). But, with that limitation, I think it definitely can, and probably will, be used clinically.

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LOWER LIMB REFLEXES OF A "CHRONIC SPINAL" MAN IN CYCLES OF MORPHINE AND METHADONE ADDICTION

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IN PREVIOUS studies * it was demonstrated that well-defined abstinence syndromes ensue when opiates are withdrawn abruptly after a period of addiction in long-surviving dogs without neocortex and in chronic spinal dogs. These, and other, data [3] indicated that the opiate abstinence syndrome involves the entire neuraxis, that, at least in part, its genesis is related to factors of little or no symbolic significance, and that the neurophysiological mechanisms that contribute to its development consist primarily of cyclic depression and excitation of certain internuncial neuron systems, with progressive augmentation of the latter process, which becomes manifest on abrupt withdrawal of the drug.

However, direct transfer of such conclusions to the explanation of drug addiction in man could be made only with reservations because of possible species differences. Studies on the effects of bilateral frontal lobotomy in man [4] revealed that interruption of thalamofrontal fiber systems reduces markedly the craving for narcotics and manipulative behavior designed to obtain such drugs ("purposive" abstinence phenomena), but this procedure has little effect on the other features of the morphine abstinence syndrome if abrupt withdrawal of morphine is carried out after the initial period of "diaschisis" has passed. These observations indicated that while the frontal lobes may exert some facilitating action on the functions of structures involved in the genesis of the "nonpurposive" features of the morphine abstinence syndrome, they did not constitute the primary site of origin of these phenomena in man. Furthermore, no inferences could be drawn from such studies with reference to the "psychogenicity" or the "organicity" of the human opiate abstinence syndrome, since "psychic" and "frontal lobes" are not equivalent terms.

Recently, however, a more definitive investigation of the sites and mechanisms of origin of the opiate abstinence syndrome in man was made possible by the admission to this institution of a former narcotic addict with almost complete physiological "transection" of the spinal cord, who was willing and legally eligible for experimental readdiction to opiates. The opportunity was utilized to study both the morphine and the methadone lower limb abstinence syndrome which ensued

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* References 1 and 2.

after abrupt withdrawal of these agents following a period of addiction to each in turn, and the "abstinence syndrome" which was precipitated by a single injection of nalorphine (N-allylnormorphine; Nalline) during addiction to morphine.† To our knowledge, no study of this kind has appeared previously in the literature.

HISTORY OF CASE

The patient, a 35-year-old Negro, gave a negative family history and had been well until 1937, when he developed a penile chancre, for which he received an incomplete course of intramuscular injections. In 1938 he was admitted to a hospital with "classical symptoms and signs of meningitis" (transcript of hospital record). These had appeared after three intravenous injections of arsenicals administered as treatment for syphilis after a positive serological reaction. At that time, examination of the cerebrospinal fluid revealed 200 cells per cubic millimeter (93% lymphocytes), 62 mg. of sugar per 100 cc., a positive Kahn reaction, and a 3333344210 colloidal gold curve. From Sept. 24 to Oct. 15, 1938, he received six intravenous injections of neoarsphenamine, the doses varying from 0.4 to 0.6 gm. He was discharged on Oct. 17, with a final diagnosis of "syphilitic leptomeningitis." The patient states that he had recovered fully except for moderate fatigability of the legs and urinary precipitancy.

He remained in this condition until the latter part of 1945, when left foot drop developed, for which a brace was prescribed. In January, 1946, he was readmitted to the same hospital because of progressive weakness of both legs. Examination revealed marked spasticity of both lower extremities, bilateral ankle clonus, knee clonus on the left, hyperactivity of all deep reflexes, and a Babinski sign, as well as confirmatories, bilaterally. The cerebrospinal fluid contained 20 cells per cubic millimeter; the spinal fluid Wassermann reaction was negative, but the colloidal gold curve exhibited a 5 reaction in the first zone. Air encephalography and air myelography were attempted, but these procedures were "unsuccessful" because of a "block in the cervical region." Between May 22 and July 25, 1946, the patient received nine combined penicillin and fever treatments at the same institution, but the lower limbs became weaker progressively.

In March, 1950, the patient was admitted to the United States Public Health Service Hospital, Lexington, Ky., for the first time because of addiction to heroin (diacetylmorphine), which he had begun to use about five years previously. He attributed his addiction to the influence of suggestions made by friends at a time when he was becoming despondent because of the increasing weakness of his legs. At the time of his admission for treatment of narcotic addiction he was able to walk short distances with assistance but relied on a wheel chair for getting about. In the hospital, withdrawal of drugs was accomplished by substituting methadone (2.5 mg. three times daily) for heroin and discontinuing the former after three days. The patient stated that after withdrawal of methadone his lower limbs "jumped" very frequently for about one month, after which he was fairly comfortable. Physical therapy was prescribed, but the patient left the institution, against medical advice, in June of the same year.

Subsequently, weakness of the legs increased progressively, and by September, 1951, his lower limbs had become completely paralyzed. He had relapsed to the use of heroin shortly after discharge from the hospital and continued to use unknown amounts daily until November, 1951, when he was arrested and confined to a penal institution. There, heroin was discontinued abruptly, and a day or two later his lower limbs began to "jump" and "pump" violently and almost continually. A physician who was called to see the patient administered some medication by hypodermic injection. This afforded no relief, and the spontaneous activity of the lower limbs continued with diminishing intensity for a period which is difficult to determine precisely. The patient stated that the "jumps" and "pumps" did not "level off" until about 45 days or longer after withdrawal of heroin. However, he was readmitted to the Lexington hospital in May, 1952, and by that time his lower limbs "jumped" only occasionally and "pumps" were very rare. Further questioning indicated that by "jumps" the patient meant spontaneous, brief adductor spasms or muscle twitches, and by "pumps," violent flexor spasms of one or both lower extremities.

† References 5 and 6.

At the time of the patient's present admission, the cranial nerves were essentially normal. In the upper extremities, muscle volume, tone, and power were normal, but the biceps, triceps, and radial periosteal reflexes were hyperactive. The ulnar periosteal reflex was absent bilaterally. Hoffmann's and Troemner's signs were present on both sides. The patient was unable to sit up without using his arms. On his sitting up, the lower part of the abdomen bulged to the left. The superficial abdominal reflexes were absent. The costal reflexes were brisk bilaterally. The symphysis pubic reflex was hyperactive on both sides, and on eliciting this reflex from either side, bilateral adductor responses were observed. In the lower extremities, muscle volume was normal, and no fibrillations or fasciculations were present. Voluntary motion was absent completely except for feeble flexion or extension movements of the lateral two toes on the left foot. "Clasp-knife" spasticity was pronounced at both knee joints. The suprapatellar and infrapatellar reflexes were hyperactive, and on eliciting these, concomitant contractions of the ipsilateral abdominal musculature were observed. Patellar clonus was present bilaterally, more constantly on the left; and ankle clonus was sustained on both sides. Pinprick stimuli anywhere on the skin of the lower extremities evoked flexor reflexes, the magnitude of which depended on the intensity of the stimulation. Crossed extensor, tibial adductor, and Philippson reflexes could be elicited on either side. The signs of Babinski, Chaddock, Gordon, Oppenheim, Rossolimo,

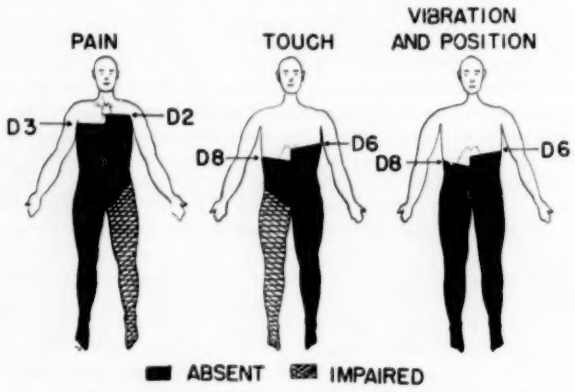

Fig. 1.—Sensory status of patient. See text for discussion.

Mendel-Bechterew, and Gonda were present in both feet. Sensory examination (Fig. 1) revealed a level to pinprick at T3 on the left and T2 on the right. Below that level, analgesia was complete over the trunk and the right lower extremity and was present patchily over the left lower extremity. Touch was impaired up to a level of T5 on the left and T8 on the right. Below that level, touch sensibility was absent over the trunk and the left lower extremity, and patchy hypesthesia was noted over the right lower extremity. Tuning fork vibrations were not perceived below the levels for touch, and position sensibility was absent bilaterally in the toes. Examination of the saddle area revealed absence of voluntary motion of the anal sphincter and anesthesia to pin and cotton. The patient stated that he still retained a vague sense of discomfort when his bladder was distended, and he was able to avoid involuntary micturition by utilizing an "auto-Credé" maneuver to empty his bladder.

Laboratory data were as follows: Lumbar puncture (lateral recumbent position) revealed an initial pressure of 160 mm. and a final pressure of 80 mm. of water. Manometric tests revealed no evidence of block. The cerebrospinal fluid was water-clear and contained 3 lymphocytes per cubic millimeter and 158 mg. of total protein per 100 cc. Pandy's test was positive, the Wassermann reaction negative, and the colloidal gold curve 0001221000. The blood Kahn test was negative, and complete blood cell counts, urinalysis, and blood nonprotein nitrogen determinations were within normal limits. An electroencephalogram revealed no abnormalities. Cystometry revealed a spastic, uninhibited "reflex" bladder, the capacity of which was 75 cc.

The neurological diagnosis was virtually complete residual upper thoracic transverse myelopathy consequent to syphilitic meningomyelitis.

EXPERIMENTAL STUDY

Methods and Materials.—During the entire period of study (seven months) the patient received no medication other than that prescribed in connection with the investigation, except for symptomatic relief of a mild upper respiratory infection and transient cystitis, when experimental observations were suspended until such therapy had been discontinued. All observations were made in a specially selected, quiet room in which the patient lay supine on a hospital stretcher equipped with a mattress made of sponge rubber or a number of blankets. To minimize reflex alterations from extraneous sources, the lower colon was cleansed by an enema in the morning, and the bladder was emptied by the patient just before and at intervals during observations, which were begun about one-half hour after a light lunch. Lower limb reflexes were elicited by use of standard neurological techniques, but of the numerous responses which could be elicited ("History of Case") only the following were quantified to a degree sufficient for the purposes of the experiment:

1. Static Quadriceps Stretch Reflex: The thigh was flexed at the hip at an angle of about 45 degrees, and the leg at the knee at an angle of about 135 degrees, the observer supporting the limb under the knee and heel. After reflex movements or changes in muscle tone consequent to the maneuver had ceased, support at the heel was removed quickly, and the time required for the heel to fall to the stretcher was measured by use of a stop watch. This procedure was repeated three times for each extremity at intervals of about one minute, and the mean "leg-falling time" was taken as a measure of the strength of the static quadriceps stretch reflex.

2. Phasic Quadriceps Stretch Reflex (Knee Jerk): The hip was flexed as above, but the limb was supported only at the knee, which was flexed passively to an extent sufficient to allow the heel to rest lightly on the stretcher. The quadriceps tendon was then tapped with an ordinary rubber "reflex hammer" 6 to 12 times with force just sufficient to elicit maximal responses. The strength of the phasic quadriceps stretch reflex was estimated in terms of 1 to 4+, and the presence or absence of quadriceps clonus was noted.

3. Nociceptive Flexor Reflex: A "pinwheel" was used to elicit this response. It consisted of a metal disc 1.8 cm. in diameter, the periphery of which was provided with 22 pointed spokes, each 0.5 cm. in length, spaced at equal intervals. The disc was mounted on an axle-bearing shaft 17.5 cm. long; the whole instrument weighed 4.85 gm. In eliciting the nociceptive flexor reflex, the pinwheel spokes were applied to the skin with force exerted by the weight of the instrument, the shaft being held at the other end with an inclination of 30 to 60 degrees to the skin, and the pinwheel was moved back and forth over the medial aspects of the thigh, leg, or foot. The strength of the nociceptive flexor reflex was estimated in terms of the average number of strokes needed to elicit it, and the magnitude of the response ("feeble," "mild," "moderate," or "marked"), after three successive trials. These were spaced at 15-second intervals when the reflex was elicited from the skin of the medial aspect of the thigh, and at 5-second intervals from the corresponding areas of the leg or foot, since it was found empirically that such intervals were necessary to insure full recovery from postreactive depression.

4. Extensor Thrust: The limb was placed in flexion at the hip, knee, and ankle, and it was supported by one hand under the knee and another that grasped the foot. After reflex activity and changes in tone induced by this maneuver had subsided, the ankle was dorsiflexed strongly and suddenly. When elicited, the extensor thrust response consisted of sudden extension at the hip and knee, chiefly the former. This reflex was graded as "absent," "weak," or "strong."

5. Spontaneous Lower Limb Activity: During portions of this study (below), testing of reflexes was omitted, and the patient was observed during continuous three-hour periods under the conditions already described. Casual conversation and short periods of sleep were permitted, but, except for a 10- to 15-minute interval in which the patient was turned on his side, he remained supine during the entire observation period. Each spontaneous movement of the lower limbs and the time at which it occurred were recorded in detail. On the assumption that the number of joints involved in spontaneous movements reflected the number of segments of the spinal cord that were activated, the following "point-score" system was devised to rate such

activity: 1 point, unilateral flexion of toes or ankle or both; 2 points, bilateral flexion of toes and ankle, or unilateral flexion of knee and ankle; 3 points, bilateral flexion of knee and ankle, or unilateral flexion of hip, knee, and ankle; 4 points, bilateral flexion at hip, knee, and ankle. In addition, 1 point was added if adductor spasm, tremors, or repetition of any of the spontaneous movements noted occurred. After each observation period, the "score" for each spontaneous movement was plotted on a time abscissa, and the total "point score" for the three-hour observation period was computed.

All drugs were prepared in aqueous solution and were administered subcutaneously. Prior to readdiction to morphine, the reflexes described were measured before and about one hour after administration of 15 mg. of morphine sulfate on two occasions, and 15 mg. of nalorphine hydrochloride in two other experiments. Experimental readdiction to morphine was begun at a dose level of 15 mg. four times daily, and this was increased gradually over a period of 37 days until a dose level of 60 mg. four times daily was attained. Addiction was continued at this dose level (except for study of acute abstinence syndromes) for 45 days, after which methadone substitution was carried out.[7] After four days of empirical adjustment of the dose, it was found that 20 mg. of methadone hydrochloride substituted smoothly for 60 mg. of morphine sulfate, and the patient was maintained on this dose four times daily for an additional period of five days. Thereafter, the daily dose level of methadone was reduced rapidly over a period of six days, after which regular injections were discontinued. However, it was found necessary to administer occasional "pick-up" injections of morphine (8 to 24 mg.) or methadone (2.5 to 5.0 mg.) during the next two weeks because of the severity of the lower limb methadone abstinence syndrome that ensued (below).

During addiction to morphine (dose level 60 mg. four times daily), observations were made after withholding the drug for 36 hours from the beginning of the 51st day of addiction, and, again, for 48 hours from the beginning of the 72d day. Between these periods, the patient was restabilized on the same dose level of morphine, and a single injection of 6 mg. of nalorphine hydrochloride was administered in one experiment, on the 57th day of addiction. After cessation of regular injections of methadone, observations were continued for 101 days.

For purposes of illustration, and as an additional means of recording the data, moving picture films of the procedures were made at intervals throughout the study.‡

RESULTS

A. Preaddiction Period.—In control observations, the strength of the static quadriceps stretch reflex varied considerably, as indicated by "leg-falling times" of about one to four seconds. Phasic quadriceps stretch reflexes (knee jerks) were consistently maximal, and transient or sustained quadriceps clonus was elicited frequently, particularly on the left. Nociceptive flexor reflexes were fairly constant. Those elicited from the medial aspect of the thigh generally appeared after two to five pinwheel strokes and consisted of "mild" to "moderate" flexion at the hip, knee, and ankle. One or two pinwheel strokes sufficed to evoke similar responses from the medial aspect of the leg, and one stroke usually evoked "moderate" to "marked" responses from the medial aspect of the foot. The technique for eliciting the extensor thrust was not developed until addiction studies were well underway; hence, control data for this reflex were obtained in the "recovery" period after conclusion of the entire study. Control data for spontaneous lower limb activity were likewise obtained only in the "recovery" period, since the need for such observations was not apparent at first. However, it was noted that such activity did not occur during periods ranging from one-half to one hour prior to admin-

‡ These moving pictures, in the form of a 16-mm. silent film (run at sound speed) approximately 1,000 ft. (300 meters) in length, are available for exhibition to medical students, physicians, and related professional groups, upon request submitted to the Director of Research, NIMH Addiction Research Center, Public Health Service Hospital, Lexington, Ky.

istration of single doses of morphine or nalorphine, when reflexes were tested, or during the hour or two after injection, when reflexes were again examined.

After administration of single doses of 15 mg. of morphine sulfate or 15 mg. of nalorphine hydrochloride, no significant changes were observed in the static or phasic quadriceps stretch reflexes. In contrast, nociceptive flexor reflexes appeared to be definitely reduced, as indicated by an increase in the number of strokes necessary to elicit a response and reduction in magnitude of the latter. This was especially marked when the flexor reflex was elicited from the medial aspect of the thigh, when 10 to 20 strokes often failed to elicit any visible response, while others were "feeble" to "mild" in magnitude. The number of strokes needed to elicit a response from the medial aspect of the leg or foot was not altered significantly, but the magnitude of the response was reduced moderately. In addition, it was noted that the limbs could be manipulated with less passive resistance and with the appearance of fewer mass reflexes after injection of single doses of either morphine or nalorphine.

B. Morphine Addiction Period.—After three days of addiction to morphine, 15 mg. four times daily, the static and phasic quadriceps stretch reflexes appeared to be essentially unchanged, but further depression of nociceptive flexor responses was observed. Twelve to 20 strokes on the medial aspect of the thigh failed to elicit any visible response. Two to 3 strokes on the medial aspect of the right leg evoked "feeble" to "mild" responses, while 12 strokes on the left side evoked no response at all. However, responses elicited from the medial aspect of the foot on either side were not significantly different from control values. Resistance of the lower limbs to passive movement continued to be decreased.

Later in the addiction period (e. g., on the 39th and 58th days of addiction, dose levels 55 to 60 mg. of morphine four times daily), further changes were noted. Quadriceps clonus appeared often when attempts were made to measure the static quadriceps stretch reflex by the "leg-falling time" method. Phasic quadriceps stretch reflexes continued to be maximal, but quadriceps clonus was elicited more frequently on both sides. Nociceptive flexor responses elicited from the medial aspect of the thigh continued to be depressed, but not as much as earlier in the addiction period. Such development of "tolerance" to the depressive effects of morphine was even more clearly apparent in responses from the medial aspect of the leg, which were practically the same as those observed in the preaddiction control studies. Extensor thrusts were easily elicited and were usually "strong" in magnitude, while practically no spontaneous activity of the lower limbs was observed during a three-hour observation period during maintained addiction to morphine (Fig. 2).

C. Morphine Abstinence Syndromes.—When morphine was withheld for 36 or 48 hours during the addiction period, "reversal" of the effects of single doses of morphine was observed. Thus, during the last 12 hours of these abstinence periods, quadriceps clonus failed to appear on testing the static quadriceps stretch reflex, and "leg-falling times" were shortened to between one-third and one second. The phasic quadriceps stretch reflexes were slightly reduced, and clonus could not be elicited. In contrast, nociceptive flexor reflexes were enhanced markedly. One stroke sufficed to elicit "moderate" to "marked" responses from the medial aspect of the thigh, as well as that of the leg or foot, and such responses were often bilateral and repetitive. At times, alternate flexion and extension of the stimulated limb was associated with reciprocal extension and flexion of the contralateral limb

for two or three cycles. On the other hand, extensor thrust responses could be elicited with difficulty, or not at all. Frequently, testing of reflexes was made difficult by adductor spasms and mass reflexes which were induced by the necessary manipulations of the lower limbs. Also, spontaneous activity of the lower limbs became very pronounced. During a three-hour observation period, 33 spontaneous movements occurred, and of these, 18 consisted of marked flexor spasms at the hip, knee, and ankle, often bilateral and sometimes alternating. Concomitantly, with the appearance of such "lower limb morphine abstinence phenomena," the patient exhibited typical features of a rather mild morphine abstinence syndrome

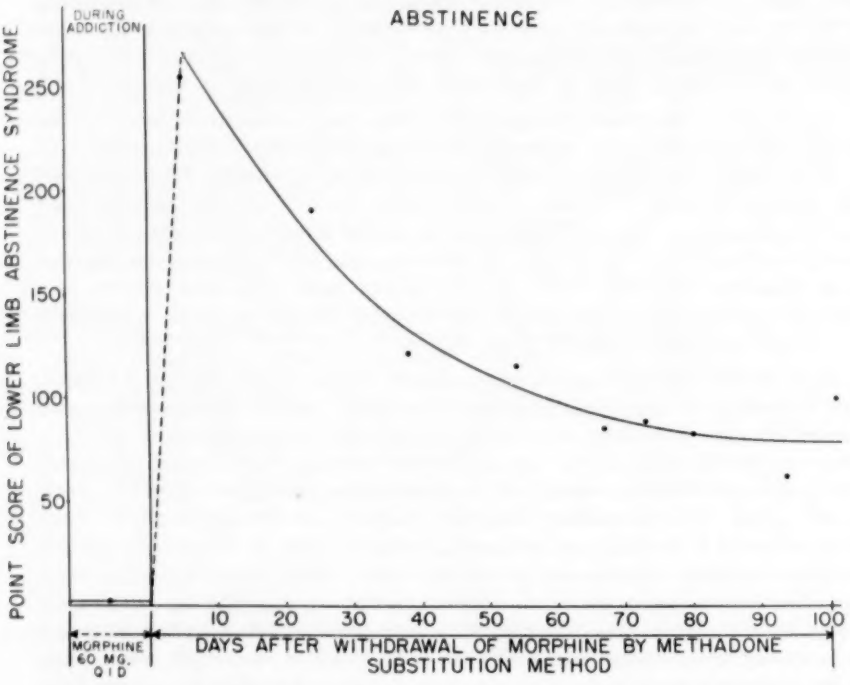

Fig. 2.—Lower limb methadone abstinence syndrome. See text for explanation of "point-score" system and discussion.

rostral to the level of physiological transection of the spinal cord, viz., yawning, lacrimation, rhinorrhea, drowsiness, and complaints of generalized muscular aching. Both the "rostral" and the "lower limb" abstinence syndromes were promptly alleviated by replacement of the patient on his regular morphine dose schedule.

The "abstinence syndrome" which was precipitated by injection of 6 mg. of nalorphine hydrochloride on the 57th day of morphine addiction (dose level 60 mg. four times daily) was much severer. During the first 20 minutes after this medication changes ensued which were practically identical with those that occurred during the 36- and 48-hour withdrawal periods. After this period, however, spontaneous prolonged rhythmic movements of both lower limbs appeared, and these

recurred periodically during the remainder of the uncontrolled "abstinence syndrome" precipitated by nalorphine. These movements consisted of regular, repetitive flexion and extension at the hip, knee, and ankle, either synchronously in the two lower extremities (reminiscent of "galloping") or alternating (somewhat like "running"). They lasted about one-half to one minute and recurred at intervals of one to two minutes. This pattern of activity tended to appear in "waves" lasting 5 to 10 minutes, separated by quiescent periods of about 10 minutes during the first hour after injection of nalorphine and less often thereafter. Defecation and urination also occurred during this time. Concomitantly, the patient exhibited severe "abstinence phenomena" rostral to the spinal level. These included yawning, lacrimation, rhinorrhea, mydriasis, goose flesh, sweating, and complaints of generalized aching and abdominal distress. About one and one-half hours after administration of nalorphine regular injections of morphine were resumed, and the changes noted began to subside within the next few hours.

D. Methadone Substitution and Withdrawal.—Substitution of methadone was carried out with little discomfort to the patient. However, when regular administration of this synthetic analgesic was terminated, abstinence phenomena were observed both rostral and caudal to the level of "physiological" transection of the spinal cord. The "rostral" abstinence phenomena were rather mild and consisted mainly of yawning, lacrimation, and rhinorrhea. They subsided within two weeks after withdrawal of methadone. In the lower limbs, however, hyperactivity of nociceptive flexor reflexes and increased spontaneous activity were observed for a prolonged period. The course of this "caudal" methadone abstinence syndrome is illustrated in Figure 2. During the first three-hour observation period (on the fifth day of abstinence from methadone), the "point score" of spontaneous lower limb activity was 255. This high value was due to numerous adductor and flexor spasms of relatively small magnitude occurring at intervals of one-half to two minutes, with only occasional maximal or bilateral flexions at the hip, knee, and ankle. Thereafter, the "point score" declined rapidly, but it did not reach a steady level until about the 90th day of abstinence from methadone, when values were in the vicinity of 82 to 88. When plotted on a time abscissa, the spontaneous activity recorded during each three-hour observation period appeared to occur in two or three "waves," but no consistent pattern was noted with respect to periodicity.

E. Recovery Period.—With respect to lower limb reflex changes, almost complete recovery appeared to have occurred about the 45th day of abstinence from methadone, when static and phasic quadriceps stretch reflexes, as well as nociceptive flexor reflexes, were very similar to those observed in preaddiction control studies. At this time, extensor thrust responses could be elicited, though not as readily as during maintained addiction to morphine. However, Figure 2 indicates that, in terms of spontaneous lower limb activity, the "caudal" methadone abstinence syndrome lasted about three months.

Formal observations were discontinued after a total of 101 days after withdrawal of methadone, or seven months after commencement of the study. To determine whether the patient's disease process had undergone any changes during this prolonged investigation, complete neurological examination and lumbar puncture were repeated. The clinical findings were identical with those observed before the study began, and reexamination of the cerebrospinal fluid revealed no significant changes:

cells, 3 erythrocytes per cubic millimeter; Pandy's test, positive; total protein, 145 mg. per 100 cc.; sugar, 59 mg. per 100 cc.; colloidal gold curve, all zeros, and Wassermann test, negative.

COMMENT

Prior to addiction, the pattern of action of single doses of morphine on the lower limb reflexes in our patient was similar to that which has been observed in chronic spinal dogs. Thus, 15 mg. of morphine depressed the nociceptive flexor reflex but had little or no effect on muscle stretch reflexes. However, certain differences between the effects of morphine in the two species were also observed. Thus, in our patient, the depressant effects of morphine on the nociceptive flexor reflex was most clearly evident when this response was elicited by the application of pinwheel stimuli to the skin of the medial aspect of the thigh. Responses from the corresponding areas of the leg or foot were less markedly depressed, while other analogs of the flexor reflex, such as the sign of Babinski and its congeners, appeared to be unaffected. The crossed extensor reflex could not be quantified satisfactorily in our present investigation, but this response could be elicited even after multiple doses of morphine. In the chronic spinal dog, the crossed extensor reflex is regularly and markedly depressed by opiates. Whether or not such differences are merely quantitative can be determined only by further studies with improved techniques for measuring such reflexes and the employment of larger doses of opiates than were used in the present study.

However, the changes in lower limb reflexes that were observed in our subject during addiction to morphine and after abrupt withdrawal of the drug were strikingly similar to the corresponding phenomena which occur in chronic spinal dogs. Thus, as addiction proceeded, stretch reflexes became hyperactive, while nociceptive flexor reflexes continued to be depressed, although the latter change became progressively less pronounced as tolerance developed. During the appearance of the morphine abstinence syndrome, stretch reflexes were depressed, while nociceptive flexor reflexes and spontaneous lower limb activity increased markedly. Furthermore, such lower limb "abstinence phenomena" were precipitated acutely in extreme form when a single dose of nalorphine was administered during maintained addiction to morphine.

It may be concluded, therefore, that the genesis of the opiate abstinence syndrome in man is related, at least in part, to processes similar to those that have been inferred to exist from data acquired by the study of various dog preparations and other species (text, above). In particular, it may be emphasized that while psychogenic factors may modify the opiate abstinence syndrome, the addict's term for this phenomenon, "kicking a habit," has more than symbolic significance. Indeed, the spinal cord phenomena described may very well be related to the muscle twitches, restlessness, and aching of which the opiate addict complains during the acute withdrawal period.

Of considerable interest, also, was the unexpectedly prolonged duration of the lower limb abstinence syndrome which followed withdrawal of methadone. In intact man this syndrome is characterized by a paucity of objectively demonstrable autonomic changes, but by a plethora of subjective complaints of "bony aching," "jumpiness," and irritability, which may continue for many weeks, or even a few months.[8] Our observations suggest that such complaints may be related to enduring physiological changes in the spinal cord.

Attention may also be drawn here to the effects of single doses of nalorphine on lower limb reflex activity prior to morphine addiction. Like morphine, this synthetic morphine derivative depressed the nociceptive flexor reflex and reduced both passive resistance to manipulation of the lower limbs and the severity of mass reflexes that were induced by such procedures. Studies on the addiction liability of this agent are still in progress,§ but it appears that nalorphine possesses this property to a slight, if any, degree. If this is verified by further research, clinical trial of nalorphine for the relief of spasticity and mass reflex activity in paraplegics may be warranted.

SUMMARY AND CONCLUSIONS

Studies relevant to problems concerning the genesis of the opiate abstinence syndrome were made on a patient with virtually complete residual upper thoracic transverse myelopathy consequent to syphilitic meningomyelitis, who had been addicted to opiates in the past and who volunteered for these experiments.

Single doses of morphine sulfate (15 mg.) depressed nociceptive flexor reflexes elicited from the skin of the medial aspect of the thigh or leg but had no effect on stretch reflexes. During active addiction to morphine (final dosage level 60 mg. four times daily), stretch reflexes became hyperactive, while partial tolerance to the depressive effects of morphine on the flexor reflex developed after an initial period of further depression. On abrupt withdrawal of morphine, stretch reflexes were depressed, while nociceptive flexor reflexes and spontaneous lower limb activity increased markedly. Such "lower limb abstinence phenomena" were promptly abolished by resumption of morphine injections.

Methadone, in a ratio of 1 mg. of this drug for 3 mg. of morphine sulfate, prevented the appearance of lower limb abstinence phenomena. On withdrawal of methadone, lower limb abstinence phenomena appeared, and these persisted with diminishing intensity for about 90 days.

Prior to morphine addiction, single doses of nalorphine (Nalline) hydrochloride, 15 mg., exerted actions on spinal cord reflexes that were similar to those of morphine: They depressed nociceptive flexor reflexes and reduced both passive resistance and the severity of mass reflexes in the lower limbs. During morphine addiction, a single dose of nalorphine hydrochloride (6 mg.) precipitated acute "abstinence syndromes," both rostral and caudal, to the level of "physiological" transection of the spinal cord that were similar to, but much severer than, those observed after abrupt withdrawal of morphine.

The lower limb abstinence syndrome in man which ensues after abrupt withdrawal of morphine or methadone following a period of addiction to either of these agents is similar to that observed in chronic spinal dogs. It is inferred, therefore, that, as in the dog, the genesis of the opiate abstinence syndrome in man is related, at least in part, to physiological changes that occur in the entire neuraxis, including the spinal cord, and that these involve primarily certain internuncial neuron systems that undergo cyclic depression and excitation during opiate addiction. Such excitatory processes increase progressively as addiction continues, and they become manifest on abrupt withdrawal of opiates, or after administration of a single dose of an opiate antagonist, such as nalorphine.

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EFFECT OF AMOBARBITAL (AMYTAL) AND AFFECT ON CONCEPTUAL THINKING IN SCHIZOPHRENIA, DEPRESSION, AND NEUROSIS

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DISORDERS of thinking are of primary significance for the diagnosis and prognosis of schizophrenia. Bleuler, Jung, and Kraepelin, among others, described these distortions of association in rich detail and considered them particularly striking manifestations of schizophrenia.

Later investigators studied this disorder of thinking with special tests.[4] Bolles and Goldstein,[2] using a modification of Weigl's object-sorting test, observed that the patients seemed "impressed by particular uses of the objects presented and do not act in terms of broader categories." Even if the examiner grouped the objects differently, the patients were often unable to verbalize the concepts. These authors concluded that "the characteristic defect of the schizophrenic patients studied was an impairment of . . . 'abstract behavior.' " Earlier, Vigotsky,[14] employing geometric solids varying in volume and color, rather than familiar objects, reached much the same conclusion. Vigotsky's results were verified in an extensive investigation by Hanfmann and Kasanin.[7] Wegrocki,[16] working with proverbs, analogies, and essential differences, concluded that "some, but not all schizophrenes, tend to manifest a disorder in the function of generalization."

The schizophrenic patient often responds to concept formation tasks, as well as other tasks, with content relevant to his personal preoccupations, although irrelevant to the task as presented by the experimenter. Cameron [3] referred to this as "interpenetration of personal themes." According to Wegrocki, "the test-situation need not represent . . . for the schizophrene, simply a trial ground for his intellectual prowess but may be fraught with affective innuendoes of which the experimenter is totally unaware." Hanfmann [6] observed with the Healy Picture Completion II test

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Gerald Rosenbaum, Ph.D., assisted in scoring the tests; L. P. Ristine, M.D., arranged for the testing of the chronic schizophrenic patients at the Mount Pleasant State Hospital, and the clinical staff of the Iowa State Psychopathic Hospital cooperated in the study.

that the patients were unable "to keep apart the sphere of personal wishes or fears, the sphere of objective reality, and the system of symbolic representation by picture or by word." Bleuler [1] summarized similar phenomena with his concept of autism, the "detachment from reality, together with the relative and absolute predominance of the inner life." These observations suggest that the most marked schizophrenic distortions occur when stimuli are present which arouse personal conflict.

PRESENT INVESTIGATION

This study is part of a larger project investigating the effects of amobarbital (Amytal) sodium and amphetamine sulfate on schizophrenic and depressive patients. Amobarbital sodium improves some patients clinically; thus it permits study of psychotic thinking in an improved state.* The purpose of the amphetamine sulfate is to combat the hypnotic effects of the amobarbital. In previous studies † significant improvement in the ability of schizophrenic patients to maintain a mental set was produced by the drugs. The effect of the drugs on conceptual thinking, however, has not been reported. Further, the role of affect in the conceptual thinking of psychiatric patients has not been studied experimentally.

In this paper, the conceptual thinking of schizophrenic, depressive, and neurotic patients will be evaluated with an object-sorting test. This test requires the subject to sort objects into groups and to report the principles on which these groupings are based.

The specific purposes of this investigation are evaluation of the following:

1. Variations in object sorting among four groups of patients: chronic schizophrenic, early schizophrenic, depressive, and neurotic

2. Effects of objects chosen to arouse affective themes on object sorting in the groups

3. Effects of the drugs on object sorting in the groups

4. Effects of the drugs and affect-arousing objects used together on object sorting in the groups

Subjects.—The patients included 24 with chronic schizophrenia (15 males, 9 females), 22 with early schizophrenia (13 males, 9 females), 21 with manic-depressive psychosis, depressive type (10 males, 11 females), and 21 with neuroses (10 males, 11 females). The mean age in the chronic schizophrenic group was 39 years, range 29 to 46 years; that in the early schizophrenic group, 26 years, range 18 to 40 years; that in the depressive group, 37 years, range 22 to 51 years, and that in the neurotic group, 30 years, range 17 to 44 years. The mean duration of illness in the chronic schizophrenic group was 12 years, range 4 to 22 years; in the early schizophrenic group 1 year, range 1 month to 3 years; in the depressive group 9 months, range 1 month to 3 years, and in the neurotic group 6 years, range 5 months to 24 years. The average educational level was approximately 12 years in all groups, with a range from 7 to 19 years. Subtype distributions in the groups were as follows: chronic schizophrenic: paranoid 6, catatonic 2, hebephrenic 2, simple 3, unclassified 11; early schizophrenic: paranoid 16, hebephrenic 3, simple 1, unclassified 2; neurotic: anxiety 4, psychasthenia 4, hysteria 3, psychosomatic disorders 2, mixed 8.

The early schizophrenic and depressive patients were tested before receiving treatment. Of the chronic schizophrenic patients, eight had received electrotherapy about two years before testing. The neurotic patients, tested after psychotherapy and just prior to discharge from the

* References 5 and 11.

† References 9 and 10.

hospital, were improved and served as relatively stabilized nonpsychotic controls. No subject was studied if there was any doubt about the diagnosis or if he had a physical disorder that interfered with testing.

Technique.—The test conditions by order of administration were as follows: (1) Neutral test, (2) Affective test, (3) Drug test, and (4) Affective-Drug test.

For the Neutral test, the subject was given 14 objects, made of four materials: wood: toy rabbit, toy ship, penholder, and three safety matches glued together; metal: table knife, letter opener, and stove bolt; paper: blotter, drawing of rabbit, drawing of spoon, and picture of wrist watch; plastic: drinking cup, small spoon, and clothes hook.

For the Affective test, the matches, bolt, hook, and picture of watch were removed and replaced by objects of the same materials. These objects, intended to arouse affective preoccupations, were selected after consulting the patient's psychiatrist and reading the case history. The affective objects for a particular patient whose problems involved religion, marriage, sex, and suicide might be, for example, a wooden crucifix, metal wedding ring, picture of breasts, and plastic gun. These objects were named by the examiner as he placed them in the test.

To administer the test, the objects were randomly placed before the patient. The instructions were:

> "Here are a number of objects which can be sorted into groups, so that we place those things together that belong together. For example, I might sort them like this." The examiner demonstrated the grouping by materials, asked the patient to state the reason for the grouping, and had him repeat this grouping himself, giving any help necessary to make the task clear. Following the demonstration, the instructions were: "This was an example of just one of the ways you could sort the objects. There isn't just one correct grouping. There are many possible ways it could be done. It doesn't matter how many objects you have in each subgroup, but every object must be used somewhere. Now I want you to group them in a different way, putting those things together that you think belong together."

Two sortings were secured; time was recorded for each. Preliminary trial showed that a third sorting made the testing time too long and produced little additional material. A five-minute time limit for each sorting appeared ample. After each sorting, the patient's reasons for making the subgroups were recorded.

The Affective test was then given. The demonstration by materials was made exactly as before; two sortings were secured, and reasons were again recorded. The instructions were as follows:

> "Now we'll start over again. I am going to change some of the objects. Since there are some new objects, you may or may not make the same groupings as before. You may use any of the principles of grouping that you used before, or any others that you may think of. What I want you to do is to put those things together that belong together."

After an average interval of seven days, the subjects repeated this entire procedure after receiving intravenous injections of amobarbital sodium and amphetamine sulfate; that is, the Drug and Affective-Drug tests were given. The average injection was 5 grains (0.3 gm.) of amobarbital sodium and 13 mg. of amphetamine sulfate. The drugs, mixed in the same syringe, were given at the rate of 1 cc. per minute until slight nystagmus was produced on lateral gaze. With subjects who developed unsteadiness and lightheadedness, testing was not begun until these symptoms subsided, usually within 15 or 20 minutes.

Each patient's cooperation was rated on a scale[9] ranging from A to E. Only patients with cooperation of C or better were included in the analysis. The cooperation ratings without drugs were as follows: chronic schizophrenic: A 1, B 18, C 2; early schizophrenic: A 1, B 16, C 2; depressive: A 2, B 14, C 4; neurotic: A 8, B 11, C 1. With drugs the ratings were as follows: chronic schizophrenic: A 2, B 17, C 2; early schizophrenic: A 3, B 16; depressive: A 7, B 13; neurotic: A 11, B 9. Thus in the present study the data for 21 chronic schizophrenic, 19 early schizophrenic, 20 depressive, and 20 neurotic patients were analyzed.

Scoring Method.—To obtain a "Principles" score, the patients' solutions were divided into three classes. Those principles involving clear-cut abstraction of good quality and fitting objectively were called Class I. These included shape, color, and function.

The following examples of Class I functional groupings are given: For the knife, cup, spoon, and picture of spoon, "utensils for eating"; for the blotter, penholder, and letter opener, "writing materials"; for the ship, rabbit, picture of rabbit, and picture of spoon, "objects for children to play with."

Objects in Class I were given 3 credits each. If the patient's principle did not fit all objects in the subgroup, credit was given for those objects to which it did apply. (This rule was applied to both Class I and Class II groupings.) For each test condition the scores from the two sortings were combined, since no systematic differences between the first and the second sorting were detectable either for diagnostic groups or for test conditions. Thus, two sortings of the 14 objects, if all were of Class I quality, permitted a maximum Principles score of 84 for any one test condition.

Class II principles were vaguer, overly general, and overly specific in formulation.

The following are examples of Class II principles: For the grouping of knife, cup, spoon, and picture of spoon, "used in the home"; "woman's, household work"; "suggest food," or "lunch service." For the grouping of blotter, penholder, and letter opener, "this is of business"; "used with ink"; "office work," or "a secretary." For the grouping of ship, rabbit, picture of rabbit, and picture of spoon, "for a child to play with in a sandpile"; "toys, ornaments, instructions," or "used in a child's room."

TABLE 1.—*Object-Sorting Principles Scores by Diagnostic Group and Test Condition*

	Diagnostic Group							
	Chronic Schizophrenic		Early Schizophrenic		Depressive		Neurotic	
Test	Mean	S. D.	Mean	S. D.	Mean	S. D.	Mean	S. D.
Neutral	25.5	12.8	30.3	12.9	39.6	18.4	37.2	13.3
Affective	29.2	20.7	32.5	13.0	33.4	23.5	38.0	14.1
Drug	22.0	14.9	29.9	15.4	34.6	13.8	42.3	14.1
Affective-Drug	21.0	14.4	25.3	13.1	31.3	17.3	33.6	15.9

Objects in Class II were given 1 credit each. For any one test condition the two sortings of the 14 objects, if all were of Class II quality, would yield a Principles score of 28.

Class III denotes absence of abstraction and received no credit. Exact repetitions of the demonstration by materials or of a subgroup previously made within the same test condition were considered in Class III. Also included here were bizarre groupings and chain-association groupings. The majority of the Class III groupings were of the latter type.

The following is an example of a Class III chain-association principle: For the hook, spoon, and matches, "These are used to cook a meal. The wife has just come home and hung her coat on the hook. She uses the matches for cooking and the spoon for stirring—no, for feeding the baby."

An example of a bizarre principle is seen in a chronic schizophrenic subject who placed the rabbit and matches together, explaining, "The rabbit being more or less polygamous; polygamous—prolific is what I mean. Three would represent matches or matings. Matings is what I said. Or [the rabbit] could be light on his feet."

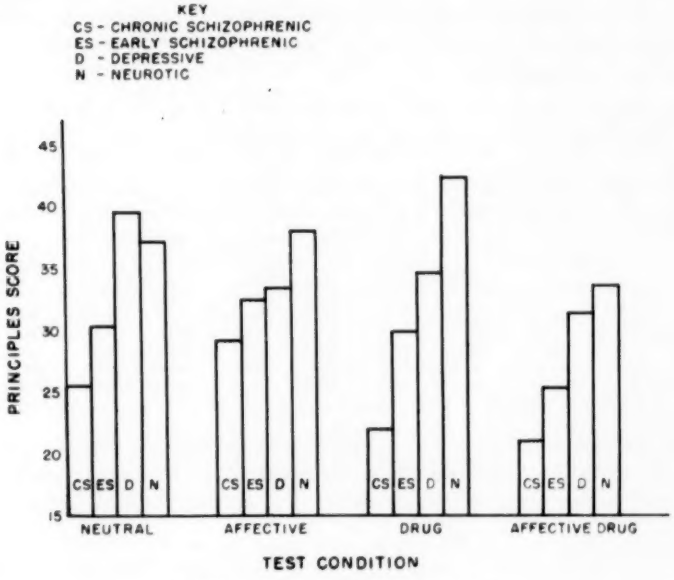
Scoring was done by two scorers, but not independently. As a check of some degree on the reliability of the scoring technique, a list of 103 scored responses considered borderline between Class I and Class II was compiled. These difficult scoring samples were classified independently by a third scorer. The percentage of agreement between his scoring and the original was 88%.

Results.—The means and standard deviations of the Principles scores are presented in Table 1 and the Chart.

On the Neutral test, analysis of variance indicated that significant differences were present among the group means ($P < 0.05$). The schizophrenic groups had the poorest performance, with the chronic group the poorer of the two (Chart).

Statistical tests of the reliability of the differences between pairs of group means were made. From these tests, the early schizophrenic group can be considered at the same level as the chronic schizophrenic group. The depressive and neurotic groups were significantly superior to the chronic schizophrenic group ($P < 0.01$ and 0.05, respectively). The depressive group was also significantly better than the early schizophrenic ($P < 0.10$). The difference between the means of the early schizophrenic and neurotic groups approached significance at the 10% level of confidence. Lastly, the depressive and neurotic groups may be considered as essentially the same.

The introduction of affective objects (Affective test) influenced the various diagnostic groups differently. Here, comparison of the Affective with the Neutral



Object-Sorting Principles Score

test yielded a significant interaction between test condition and the diagnostic groups variable ($P < 0.001$). No one group by itself, however, changed significantly from the Neutral to the Affective test. The only downward shift was in the depressive group; this decrement approached, but did not reach, significance at the 10% level. Thus, the significant effect of the affective objects was due more to differences in direction of changes for the various groups than to the magnitude of change for any one group. Groups other than the depressive maintained the same relative performance levels as on the Neutral test.

The effects of the drugs alone were evaluated by comparing the Neutral and the Drug tests. Here, again, the interaction between test condition and diagnostic group was significant ($P < 0.001$). Thus the drugs affected the groups differently. The two schizophrenic groups were slightly, but not significantly, poorer on the Drug than on the Neutral test, and the depressive group was significantly poorer

($P < 0.10$), while the neurotic group was significantly better ($P < 0.10$). Therefore the effect of the drugs was due to differences in both direction and magnitude of changes in the diagnostic groups.

When the Neutral and the Affective-Drug conditions were compared for all groups considered together, Affective-Drug performance was reliably lower than Neutral performance ($P < 0.01$). There was, however, no statistically reliable difference among the groups in the amount of decrement. All groups achieved poorer Principles scores on the Affective-Drug test than on any other condition.

Comparison of the Affective-Drug test with the Affective test showed that all groups were poorer with drugs, but the magnitude of the decrement differed among the groups. That is, the interaction between test condition and diagnosis was significant ($P < 0.01$). For both schizophrenic groups the decline from the Affective to the Affective-Drug test was significant ($P < 0.10$) and was about twice that for either the depressive or the neurotic group. In the latter two groups the drop was not significant.

The magnitude of the decrement from the Drug test to the Affective-Drug test was also significantly different for the various groups ($P < 0.001$). The only group

TABLE 2.—*Object-Sorting Time Scores, in Seconds, by Diagnostic Group and Test Condition*

	Diagnostic Group							
	Chronic Schizophrenic		Early Schizophrenic		Depressive		Neurotic	
Test	Mean	S. D.	Mean	S. D.	Mean	S. D.	Mean	S. D.
Neutral	182.1	131.6	199.5	132.0	232.5	143.8	161.2	81.8
Affective	182.6	147.3	204.0	127.1	272.2	162.7	139.2	64.2
Drug	165.0	112.7	146.6	126.3	149.8	86.9	100.5	62.3
Affective-Drug	178.1	138.1	182.6	108.4	196.0	103.5	129.0	87.7

for which the amount of drop was significant was the neurotic group ($P < 0.05$). It may be seen in the Chart that the performance of the neurotic group was at its highest level on the Drug test, while no other group had its peak performance on that test.

The distributions of the Principles scores show the percentages of schizophrenic and depressive patients who were impaired relative to the neurotic group. On the Neutral test the poorest score in the neurotic group was 19; 43% of the chronic schizophrenic, 16% of the early schizophrenic, and 15% of the depressive patients scored lower. On the Affective test the poorest score in the neurotic group was also 19; 43% of the chronic schizophrenic, 11% of the early schizophrenic, and 30% of the depressive patients had poorer scores. On the Drug test the poorest score for the neurotics was 24; 57% of the chronic schizophrenic, 32% of the early schizophrenic, and 25% of the depressive patients were poorer. On the Affective-Drug test the poorest score for the neurotics was 14; 33% of the chronic schizophrenic, 21% of the early schizophrenic, and 5% of the depressive patients had poorer scores. This material indicates the wide overlap in the scores, and therefore the impossibility of making categorical statements about concept-formation ability for diagnostic purposes.

The means and standard deviations of the time scores for the four test conditions, by diagnostic groups, are presented in Table 2. All groups were consistently

faster on the tests with drugs than on those without drugs, the Drug test producing the shortest response times. The neurotic group was consistently the fastest on each test condition. The depressive group was the slowest of the four groups on both nondrug tests, but speeded up most from the nondrug to the corresponding drug tests.

The relation of the Principles score to level of cooperation, duration of illness, age, and intelligence was analyzed.

On the Neutral test cooperation rating and Principles score were positively correlated (r, $+0.34$). With drugs this correlation was the same. No relation was found between the change in cooperation from Neutral to Drug test and the corresponding change in test score (r, $+0.02$). The magnitude of these correlations indicates a minimal influence of cooperation. It will be remembered, however, that a cooperation rating below C excluded a patient from the analysis.

No relation was found between Neutral Principles score and duration of illness. The r of -0.14 was not significantly different from zero. The same was found for age (r, -0.13, not significant).

Intelligence level was measured by a short form of the Wechsler-Bellevue Verbal Scale, including Information, Comprehension, and Vocabulary. These subtests were chosen because they are least subject to impairment associated with age.[15] The mean nondrug Verbal IQ's were 104 for the chronic schizophrenic, 112 for the early schizophrenic, 116 for the depressive, and 117 for the neurotic group. A correlation of $+0.34$ was obtained between the Neutral Principles score and nondrug Verbal IQ. Thus, while a general intellectual factor was operating, it accounted for only 12% of the variance in the Neutral Principles score.

COMMENT

The results of the Neutral test confirm previous conclusions that there is a deficit in conceptual thinking in schizophrenia, since the two schizophrenic groups performed at a lower mean level than the depressive and neurotic groups. This deficit was somewhat more marked in the chronic schizophrenic group. The Principles score alone, however, as a measure of conceptual thinking, does not provide sufficient discrimination to be a reliable diagnostic indicator of schizophrenia; witness the wide overlap in scores among the groups.

The introduction of objects intended to arouse affective themes and the use of drugs each produced alterations in conceptual thinking. The influence of these two variables differed among the diagnostic groups. The schizophrenic groups did not show significant impairment with either affective stimuli alone or drugs alone. Apparently, the thinking disorder in schizophrenia, as measured by the Principles score, is relatively impervious to either of these manipulations separately. The effect of amobarbital is possibly in line with a previous study of schizophrenic patients,[11] which reported no change under amobarbital in the "structure of delusional ideas." When drugs and affective objects were used together, the schizophrenic groups dropped in performance. This suggests that the drugs weaken the ability to conceptualize, thereby permitting affective material to disrupt thinking. An alternative hypothesis is that the drugs release affective preoccupations, which, in turn, impair concept formation. In this connection, several chronic schizophrenic patients (not included in the results reported here) "broke down" so markedly under the drugs that they could not be tested. These patients became apprehensive.

tearful, or hostile and made a variety of defensive and withdrawal responses to escape from the test situation. Whatever the explanation, it seems that the basic schizophrenic thought disturbance can be intensified under drugs when affective stimuli are present.

The depressive group, which performed at the highest mean level on the Neutral test, can be regarded as relatively unimpaired if the neurotic group is considered a control. The depressive group, in contrast to the other groups, proved vulnerable to the effects of each experimental variable. This was the only group showing poorer conceptual thinking when either drugs or affective objects were introduced separately. As in the other groups, the simultaneous introduction of the two produced poorest performance. After injection of the drugs, the examiners noted that the depressive patients spontaneously expressed their affective preoccupations; this was in striking contrast to their behavior without drugs. Again, as in the schizophrenic groups, the relative stability of the conceptualizing process and a more intense reaction to affective material may be considered. The experimental and behavioral evidence suggests that the increased prominence of affective reactions was the more important factor in producing impairment in the depressive group.

In response time, the depressive group speeded up much more from the Neutral to the Drug test than did the other groups (Table 2). This speeding is consistent with clinical observation [5] and with our previous report on these same groups [9] that reaction times of depressive patients, in contrast to those of the other groups, were faster with the drugs.

The neurotic patients, when the affective objects were introduced, showed no change in Principles score. With drugs alone, contrary to the other groups, they improved in thinking. In common with the other groups, they performed most poorly when affective objects and drugs were used simultaneously. The failure of the affective stimuli alone to modify the Principles score implies that the specific defenses against affective stimuli in neurosis permit relative stability of the conceptual process. The improvement of this group on the Drug test suggests a lessening of a generalized constriction of thought. This generalized constriction is probably a by-product of the specific neurotic defenses. It operated in the Neutral test to produce a lower Principles score than in the Drug test. Presumably, in the Affective test a generalized constricting factor was also at work, as well as the specific defenses related to the affective stimuli. The weakening of a generalized defensive constriction by drugs, as proposed here, is similar to the suggestions of other writers.‡ With the generalized defensive constriction weakened by drugs, the specific neurotic defenses are no longer sufficient, and affective stimuli can then cause an impairment of conceptual thinking, as is seen in the Affective-Drug test.

The results of this study indicate that the groups can be scaled as to modifiability of thinking in response to experimental manipulation. The schizophrenic groups are least modifiable in that they changed only on the Affective-Drug test. The depressive patients are most easily modifiable in that they changed on the Affective test as well as on both drug tests. The neurotic patients show an intermediate degree of modifiability, changing on both drug tests but not on the Affective test.

‡ References 8 and 11-13.

We should like to emphasize that this discussion is based on group trends. Some individual patients went contrary to the group trends; some were more influenced by affective stimuli, or by drugs, or by the combination, than were others. Some neurotic patients performed more like depressive patients, and some schizophrenic patients, more like neurotic patients. More specific experimental analysis is necessary to clarify the factors underlying these wide individual variations. For example, one might study the relation between intensity of affective stimuli and the degree of impairment of conceptual thinking. Also, different methods of analyzing the protocols to assess qualitative features are worth exploring. Although the level of thinking as measured by the Principles score showed no change for the schizophrenic groups when the affective objects were introduced, striking instances of personalized response modes often appeared.

SUMMARY AND CONCLUSIONS

Conceptual thinking was studied with a new object-sorting technique in four groups of hospitalized patients: chronic schizophrenic, early schizophrenic, depressive, and neurotic. There were four test conditions: (1) Neutral test, (2) Affective test, in which objects intended to arouse affect were introduced; (3) Drug test, which was the same as the Neutral test except that each patient received amobarbital (Amytal) sodium and amphetamine sulfate intravenously, and (4) Affective-Drug test, in which both affective objects and drugs were employed. A Principles score was devised to measure the level of conceptual thinking.

On the Neutral test the schizophrenic groups performed more poorly than the depressive and neurotic groups. When affective objects alone were introduced (Affective test), performance became poorer in the depressive group but remained essentially unchanged in the other three groups. When drugs alone were used (Drug test), the schizophrenic groups showed no change from their Neutral test level of performance. Both nonschizophrenic groups, however, changed significantly with drugs, the performance of the neurotic group being facilitated and that of the depressive group impaired. When drugs and affective objects were introduced simultaneously, all groups showed impairment in thinking as compared with that on the Neutral test. This was the only experimental condition to which the schizophrenic groups showed a significant change from the Neutral test.

These results suggest the following conclusions:

1. Schizophrenic patients show impairment in conceptual thinking relative to depressive and neurotic patients. In view of the wide overlap in scores among the groups, it is doubtful whether measures of conceptual thinking can be used as reliable diagnostic indices.

2. Conceptual thinking in schizophrenia is resistant to change, so that neither affective stimuli nor drugs alone can modify it. Further impairment occurs only when the two are presented simultaneously. Under the conditions of this experiment it appears that in schizophrenia the effects of the drugs on conceptual thinking depend specifically on the presence of affective stimuli.

3. Conceptual thinking in depression is relatively adequate in quality under neutral testing conditions, but is easily impaired by affective stimuli or drugs. The impairment seems related to the increased prominence of affective preoccupations.

4. The thinking of neurotic patients appears constricted in neutral situations. The introduction of affective stimuli does not impair their conceptual thinking. Drugs apparently lessen their constriction and facilitate conceptual thinking in neutral situations, but disrupt their thinking in affective situations.

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INCIDENCE OF IDIOPATHIC CONVULSIONS IN LATER LIFE

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ALL PAPERS dealing with idiopathic convulsive states admit the fact that such seizures may have their onset in adult life, and every physician treating any appreciable number of such patients will realize that the initial development of idiopathic convulsions in late life is not rare. However, certain traditional statistics have been preserved in almost all textbooks covering the subject, with little change in the past 60 years. These figures represent the usual medical school teaching and are firmly rooted in the minds of most of us. Grinker [1] states:

> Chronic epilepsy probably begins with greatest frequency in the first years of life. There is then a fall in the number of cases beginning from the ages 1 to 5, an increase from the 4th to the 7th years, a decline in the 8th and 9th years and a steady increase from 12 to 15 years.

This author cited Turner, who stated that one-fourth of the cases have their onset at ages of 11 to 15, one-half at ages of 11 to 20, and three-fourths before the age of 20. The Craig Colony statistics [1] showed onset in 75% before the age of 20. Other representative texts give the following: Brain,[2] "three-fourths of all cases . . . under age of 20"; Wilson,[3] "59.4% before age 20 and 78% before age 25," and Wechsler,[4] "vast majority before age of 20." Neilsen [5] stated:

> The time of onset of seizures varies and epilepsy without a demonstrable gross focus may appear even late in life. However, in seizures beginning after the age of 30, the physician should expect to find a definite etiology, such as alcoholism, cerebral neoplasm, aneurysm, physical anomaly or trauma.

Cross [6] stated:

> Idiopathic epilepsy, as is well known, makes its appearance in a large percentage of cases in childhood or during adolescence though rarely it may appear later.

He repeated the popular figure of 75% of cases starting before the age of 20 and went on to cite the data of Gowers, in which the latter showed that 89.5% of patients had the onset of convulsions within the first 29 years of life, concluding that "in general, epileptiform attacks of late development are symptomatic of some definite underlying pathological condition."

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Nattross [7] quoted from Osler's "Medicine": "It is well always to be suspicious of 'epilepsy' beginning in adult life, for in a majority of such cases the disease is not epilepsy." This author went on to publish data from a series of 602 cases, which were analyzed as follows:

TABLE 1.—*Data on 602 Cases of Epilepsy with Onset in Adult Life*

Age, Yr.	Number	Percentage
0-10	133	22
11-20	185	31
21-30	131	22
31-40	72	12
Over 40	81	13

While Turner's [1] results showed only 9 to 10% of cases in which the first idiopathic seizure occurred after the age of 30, Nattross' series showed 25%, leading him to conclude that idiopathic epilepsy is by no means uncommon in persons of mature years.

One can have no argument with Osler's recommendation of viewing each such case with suspicion, but it is my opinion that a considerable percentage of these patients are proved to have idiopathic convulsions, a percentage distinctly higher than the figures generally accepted. Such patients should be examined exhaustively to rule out serious organic pathology, but it is also true that paroxysmal convulsive disorders in childhood and adolescence deserve equally intensive investigation before one accepts a diagnosis of idiopathic epilepsy.

For obvious reasons, this report does not attempt to establish definite figures for the age of onset of epilepsy. The patients discussed were all male veterans over 20 years of age. A certain amount of screening out of epileptics had already been done by the induction physical examinations, although many inductees deliberately concealed the history of convulsions. Also, with the widespread interest in establishing service connection for their condition, it is recognized that many may have falsified their past medical history. This factor has been minimized by obtaining information from the family and other outside sources, civilian and military medical records, analyses of school and employment records, and any other corroborating source. The paper does attempt to emphasize the relatively frequent incidence of essential epilepsy beginning in the third or fourth decade of life.

Each case included in the series has been followed personally by me for periods varying from one to five and one-half years. Some of these have been followed in the hospital for much longer, up to 25 years. Each patient coming to the hospital for the first time with the report of convulsive seizures routinely has a complete history, physical and neurological examination, psychiatric evaluation, investigation of outside environment by social service workers, skull x-rays, electroencephalogram (including sleep records and use of pentylenetetrazol [Metrazol] where indicated), fasting blood sugar and nonprotein nitrogen determinations, and lumbar puncture, with manometric readings and complete examination of cerebrospinal fluid. Electroencephalographic and neurological examinations were repeated on all subsequent visits, together with any or all of the other examinations, as indicated. Where any localizing neurological findings or focal electroencephalographic abnormalities were found, neurosurgical opinion was obtained and a pneumoencephalo-

gram or ventriculogram was obtained if the neurosurgical consultant deemed it justified. In eight cases the diagnostic evaluation included exploratory craniotomy without any lesion being demonstrated.

In order to eliminate the possibility of convulsions due to precocious cerebral arteriosclerosis, no patient was included in the series who had onset of seizures at an age greater than 45 years. Also excluded were all patients with central nervous system syphilis, brain tumor, congenital brain abnormalities, convulsions following known encephalitis or meningitis, a proved history of head injury or of heavy metal poisoning, or chronic alcoholism.

Each patient included in the series was seen by more than one member of the full-time or consultant staff in neurology or psychiatry, and many were seen by the neurosurgical service. The diagnosis of idiopathic epilepsy was made only when the history was reasonably typical and when a thorough investigation failed to reveal neurological pathology or generalized somatic disease to account for seizures. Each patient being studied initially because of convulsive seizures spent a minimum of 30 days as an inpatient on the neuropsychiatric service, and longer if indicated. All patients were kept under observation long enough, or reexamined frequently enough, that at least one seizure was witnessed by professional personnel having

TABLE 2.—*Distribution of Cases of Epilepsy According to Age of Onset*

Age of Onset, Yr.	No. of Cases	Percentage
Birth to 20	46	21.69
21 to 30	125	58.97
31 to 40	41	19.34
	212	100.00

adequate experience in the characteristic picture of grand mal, petit mal, or psychomotor phenomena. Where there was any real reason to believe that attacks represented a dissociative reaction or conversion reaction, the diagnosis of paroxysmal cerebral disorder was not made. Each patient was recalled to the hospital at least three times, usually at intervals of three months, six months, and one year, for reexamination and reevaluation of therapy, and many have had multiple readmissions, as well as study elsewhere.

Of all patients entering this hospital with the history or findings of convulsive seizures, 216 met all the criteria described above. Since only four of these patients fell in the age group of 40 to 45 years, their cases were discarded so that data could be presented by decades, as shown in Table 2.

A comparison of Table 2 and Table 1 shows a great difference in the percentage of cases with onset in the years between 20 and 40. Some of the reasons for this increase over Nattross' statistics are indicated in the body of the paper. However, the difference between percentages in Table 2 and the usual "75% before age 20" is so marked as to make it significant.

SUMMARY AND CONCLUSIONS

Data are presented to reemphasize that the onset of convulsions in later life is not presumptive evidence of organic brain disease and that the incidence of such phenomena in persons of more mature years without demonstrable pathology is by no means uncommon.

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SUPRASCAPULAR NERVE SYNDROME AS REVEALED BY NEW (ANTERIOR) APPROACH IN INDUCTION OF BLOCK

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MY INTEREST in the suprascapular nerve stems from the year 1946, when I encountered in rapid succession three cases of causalgia with phantom limb and spasms in arm stumps, attaining permanent relief in all by alcohol block of the suprascapular nerve.[1] One of these patients reported recently to show me the latest type of artificial limb he was using. He has had no recurrence of the painful phenomenon in the 8 years. However, finding the standard posterior approach too involved, I sought a more facile anterior approach, with the result shown in the Figure, in which the nerve is all but subcutaneous (subfascial). With the incentive offered by this handier approach, I have studied 50 cases of suprascapular neuritis through the 8-year period since the occurrence of this case. From these data (Tables) there emerges a definite syndrome.

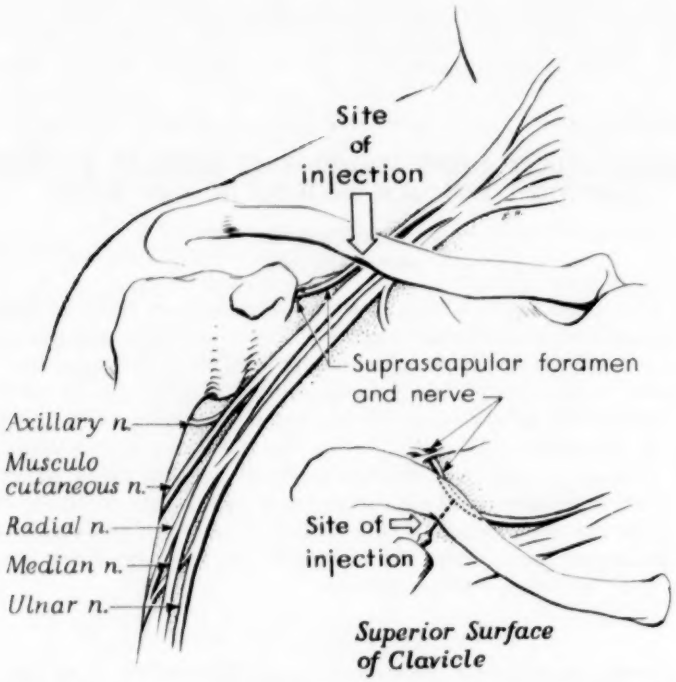
SUPRASCAPULAR NERVE SYNDROME

The patients come into the office complaining of brachialgia of varying degree and extent, and the arm is usually bound to the side by reflex muscle spasm. Upward drag by the skin at the clavicular angle (Figure) is painful. Wincing tenderness on the affected side is elicited by pressure with a blunt probe at this angle and at about the middle of the supraspinatus muscle and upon the infraspinatus muscle, in line with the upper spot. These spots on the spinati are marked with iodine. After the suprascapular nerve is blocked with a drop or two of alcohol, pressure on these three spots will no longer elicit wincing. They are hyperesthetic puncta in the descending portion of the inflamed suprascapular nerve, and not "fibrositis" spots. Immediately after injection the patient usually can abduct and elevate his arm throughout the full range of 180 degrees and all subjective pain vanishes.

The most probable cause of inflammation of this nerve is "string-sawing" irritation in its foramen, which irritation may spread to and involve the lateral and posterior cords of the brachial plexus (Figure). (It might be profitable to examine these foramens and their transmitted nerves in a series of cadavers.)

ILLUSTRATIVE CASE.—A man who had operated an electric drill had begun to complain of pain in the left shoulder four months previously. There were (Figure) wincing tenderness at the clavicular angle and over both spinati 5 cm. lateral to the vertebral border of the scapula (suprascapular nerve); pain over the lateral surface of the deltoid muscle (axillary nerve), at times radiating to the lateral portion of the elbow and the styloid process of the radius (radial nerve), and, at times, inability to make a fist (median nerve).* He could not abduct the arm beyond

* Thus, only the lateral and posterior cords of the brachial plexus are subject to irritation by the traction of the suprascapular nerve.



The author's anterior approach in induction of block of the suprascapular nerve en route to its foramen (hawsehole) and anchorage in the spinati: its windlass (brachial plexus) is relatively immobile and is irritated by tugging on or foraminal string-sawing of the nerve cable, causing brachialgia. The inset (lower right) shows the clavicular angle at the concavoconvex junction of the anterior border of the clavicle where the needle enters. The illusion that the needle is being passed to a high level may be dispelled by reference to the upper diagram, where its point should be directed only 1 or 2 mm., above and behind the posterior border of the bone and 1 cm. more or less in depth until parasthesia is obtained.

TABLE 1.—*Etiologic Factors*

No. of patients	50
Males	20
Females	30
Right side	21
Left side	29
Causes	
Machine throwing arm to and fro	2
Electric drill shaking arm	1
Turning a stuck wheel	1
Reaching above head to shelf	1
Reaching out to check another person from falling	2
Lifting a heavy object, such as baby	2
Exposure of shoulder to draft (riding with car window open)	2

60 degrees, at which point "something began to pull" over the subdeltoid bursa (axillary nerve). All these spots were marked with iodine. After alcohol block of the suprascapular nerve at the clavicular angle, pressure upon them no longer elicited wincing tenderness; all subjective pain vanished, and all muscles relaxed, so that the patient could then move his arm freely in all directions, "dig his fingers" into his palm, comb his hair, and don two shirts, a vest, a coat, and an overcoat, without pain. Three years previously he had had a similar attack on the same side, which also cleared up immediately after nerve block, and the present attack is the only recurrence.

Technique.—From the sternal head of the clavicle the tip of the index finger is passed along the anterior border until it encounters a notch, where the bone begins to bend forward (Figure,

TABLE 2.—*Syndromes and Signs*

Pain from acromion downward along extensor surfaces to fingers	12
Limited abduction and elevation of arm	20
Limited retraction of arm	1
Aching over deltoid	3
Pectoral pain	2
Constriction of respiration	1
Pain at clavicular angle on raising arm	1
Patient points to pain at clavicular angle	13
Causalgia in no-stump limb	1
Pins and needles sensation in fingers	3
Numbness in fingers	4
Coldness in fingers	4
Difficulty in donning coat or arranging hair	30
Difficulty in making fist	10
Severe pain on using electric drill	2
Severe pain on painting or hammering	1
Severe pain on bowling	1
Severe pain on ironing	1
On point pressure at clavicular (injection) angle, pain radiates	
(*a*) Up into neck or down into arm	12
(*b*) To finger tips	12
(*c*) Reproduces patient's pain complaint	8
(*d*) Reproduces pins and needles sensation in fingers	1
Wincing spots	
(*a*) At clavicular angle	50
(*b*) Over supraspinatus	44
(*c*) Over infraspinatus	44
Needle entering nerve	
(*a*) Radiates pain up into neck or down into arm	10
(*b*) Reproduces patient's pain complaint	4
(*c*) Reproduces pins and needles sensation in hand	1
Pain at clavicular angle on dragging skin upward	35

below)—the clavicular angle—into the apex of which the fingernail exactly fits. A vertical line is then imprinted on the skin by the nail. The skin is held taut and daubed with iodine, and the needle is entered perpendicularly to the surface exactly at the apex of the notch and passed backward until it clears the lower border of the bone. The syringe barrel is now lowered about 10 degrees; the needle is felt penetrating the deep fascia as it advances, and the nerve is gingerly sought 1 or 2 mm. deep to the deep fascia, usually being located by radiation of pain upward or downward as the needle enters the nerve. Whereupon a minim or two of alcohol is injected. The nerve is usually met with ⅜ in. (0.95 cm.) below the surface of the skin. Should the nerve not be encountered on the first few trials, the alcohol may be injected, with an excellent chance of attaining paraneural infiltration. Alternatives are a durable nonalcoholic injection medium and the posterior approach.

COMMENT

Implication of the suprascapular nerve in this syndrome seems to be corroborated by the wincing pain elicited by blunt-point pressure upon it at the clavicular angle and in its descending course through the spinati, as well as by radiation of pain

upward or downward as the needle enters the nerve (Table 2). Thus, in the patient who complained of a pins-and-needles sensation in the hand this form of paresthesia was intensified both by point pressure at the clavicular angle and by entrance of the needle into the nerve, and was relieved by alcohol block of the latter. Curiously enough, there has been no evidence of paralysis or wasting of the spinati in any of these cases in which alcohol was used.

The sympatholytic action of suprascapular nerve block was exhibited in warming of the fingers in four cases and in the relief of causalgia in the intact limb and in the three stump cases, and is probably due to the release of the brachial plexus from irritative traction. It was also manifest in the obturator nerve in three cases of thigh stumps with causalgia, phantom limb, and spasms, which likewise were

TABLE 3.—*Immediate Results*

All pain vanished	36
Free and complete abduction and elevation of arm	20
Relaxation of fingers	10
Painless donning of shirts and coat (men)	25
Facility in arranging hair (women)	35
Vanishing of wincing spots from spinati	44
Vanishing of causalgia (only 1 no-stump case)	1
Vanishing of numbness in fingers	1
Vanishing of pins and needles sensation from fingers (only 1 case)	1
Vanishing of left pectoral pseudoangina	4
Hand felt warmer	4
Facility in deep-sea fishing for first time in many years	1

permanently relieved in 1946 by alcohol block of the obturator nerve. The thigh stump patient † ultimately dispensed with crutches in favor of an artificial limb.

Many cases of brachialgia, from pins-and-needles sensation to extensive involvement of the lateral and posterior cords, will yield to block of this nerve.

SUMMARY

A new (anterior) approach to the suprascapular nerve for the induction of block is described which facilitates and encourages the study of the symptoms and signs of inflammation of this nerve, setting up a constant pattern which establishes itself into a syndrome. The technique is given. Analyses of the 50 cases are included (Tables 1 to 3).

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† Skillern,[1] p. 458.

SUCCINYLCHOLINE CHLORIDE IN ELECTROSHOCK THERAPY

II. Cardiovascular Reactions

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IN THE preceding paper, clinical data were presented concerning electroshock therapy in conjunction with administration of the muscle-relaxant drug succinylcholine chloride. Some of the other muscle-relaxant drugs have a definite effect directly on the autonomic system and thus indirectly on the circulation. Tubocurarine (*d*-tubocurarine) chloride is said to produce partial blockade of the autonomic system,[1] while gallamine (Flaxedil) initiates a tachycardia through its inhibiting effect on the cardiac vagal fibers.[2] Tubocurarine chloride also produces a decrease in systemic blood pressure which is not prevented by atropine. This effect is thought to be partially related to its autonomic ganglion-blocking properties and partially to a histamine liberation.[3] The latter property is responsible for the bronchospasm which is occasionally seen in clinical anesthesia. Although succinylcholine is closely related chemically to the ganglion-blocking (hypotensive) methonium drugs and to acetylcholine, previous workers [4] have been unable to show any adverse effect on cardiovascular dynamics in man or animals. Neither histamine-liberating effects nor any effect on transmission in the autonomic nervous system has been demonstrated. Adderley and Hamilton [5] have reported a rise in both systolic and diastolic blood pressure following the administration of succinylcholine. Bankhead, Torrens, and Harris [6] have reported a very careful evaluation of the cardiac arrhythmias following electroshock treatment. They noted ventricular premature contractions, bigeminy, nodal rhythm, and bradycardia. Atropine, cardiac drugs, and oxygen (prevention of asphyxia) were recommended in the prevention and treatment of adverse cardiac reactions.

Although electroshock therapy is usually considered to be a very benign form of treatment, occasional fatalities and near fatalities do occur.* Since many of the

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Supplies of succinylcholine chloride (Anectine Chloride) were made available by Dr. Donald S. Searle, Director of Medical Research, Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y.

* References 7, 8, 9, 10, and 11.

patients requiring this form of treatment are in the older age group, with various forms of cardiovascular disease, prevention of abnormal cardiac responses is important

METHODS

We have previously outlined the method of treatment utilized in this series, including the doses of thiopental (Pentothal) sodium and succinylcholine chloride. All patients receiving these drugs were respirated with 100% oxygen during the treatment. Electrocardiographic tracings and blood pressure recordings were made before, during, and after the treatment. It is the purpose here to analyze the results obtained and determine their significance with relation to cardiac function.

In order to eliminate as much as possible the many variables which may be present in clinical investigation, we established seven groups of patients for study. These groups are shown in Table 1.

TABLE 1.—*Group Differentiation*

Group	No. of Patients	Treatment
I	80	Both thiopental sodium and succinylcholine chloride
II	31	Thiopental sodium alone
III	38	Succinylcholine chloride
IV	40	No drugs
V	13	All four of the above treatments used at least once during course of therapy
VI	16	Effect of atropine on Group I
VII	10	Thiopental-tubocurarine chloride

TABLE 2.—*Cardiac Arrhythmias in Electroshock Therapy*

Group	Technique	No. Patients	% Pre-treatment	% After Thiopental	% After Succinyl-choline	% After Electro-shock
I	Thiopental-succinylcholine-electroshock	80	8.7*	17.5†	21.5‡	42.50§
II	Thiopental-electroshock	31	3.2*	16.1†	....	34.21‖
III	Succinylcholine-electroshock	38	2.6*	....	10.5¶	81.33#
IV	Electroshock	40	5.0*	....	....	32.50**
VI	Atropine 0.4 mg.....	16	12 (2 pts.)	18	31	56.00††
	Atropine 1.5 mg.....	16	6 (1 pt.)	12	12	25.00‡‡

Statistical Analysis:
* Pretreatment: not significant.
† After thiopental: significant increase ($P = 0.05$) over *.
‡ After succinylcholine: increase significant over * and ¶ but not over †.
§ Significant increase over ** and ‖ ($P = 0.01$).
‖ Decrease compared with §: significant ($P = 0.01$) but increase over ** not significant.
¶ After succinylcholine: significant increase ($P = 0.05$) over *.
# Significant increase over **, ‖, and § ($P = 0.01$).
** Significant increase ($P = 0.01$) over *.
†† Control values on atropine 0.4 mg.
‡‡ Significant decrease from †† ($P = 0.01$).

Analysis of the material obtained from this work indicated that many of the changes noted might be of vagal origin. In the sixth group, 16 patients were treated with thiopental sodium-succinylcholine chloride-electroshock. Prior to one treatment, the patient received 0.4 mg. of atropine sulfate subcutaneously, while at a later treatment he received 1.5 mg. We chose 0.4 mg. of atropine sulfate as the "control" dose, as our previous work had been performed with this premedication.

INTERPRETATION OF DATA

Cardiac Arrhythmias.—The data concerning cardiac arrhythmias are summarized in Tables 2 and 3. Table 2 requires a notation in that each vertical column is a cumu-

lative figure and includes those arrhythmias of the previous figure. Therefore, the postconvulsive incidence for each group is the total incidence. As can be noted from this Table, the percentages of arrhythmias in the pretreatment period of the four groups correlate well; that is, the groups are not dissimilar from the electrocardiographic standpoint. After thiopental sodium, Groups I and II reveal the same incidence of arrhythmias. Succinylcholine chloride was accompanied by only a very slight increase in incidence of arrhythmias over that seen to follow thiopental sodium. In those patients receiving succinylcholine chloride without a preliminary hypnotic drug, the incidence was increased from 2.6 to 10.5%. Postconvulsive arrhythmias are indicated in the final column. The frequency and type of EKG abnormalities are summarized in Table 3. Most of the patients showing arrhythmias in the pretreat-

TABLE 3.—*Type of EKG Abnormalities and Their Relative Frequency in Electroshock Therapy*

	Shock Only (40 Patients)		Thiopental-Shock (31 Patients)			Succinylcholine Shock (38 Patients)			Thiopental-Succinyl-Shock (80 Patients)				
Type EKG Abnormality	Pretreatment	Postshock	Pretreatment	Post-Thiopental	Postshock	Pretreatment	Postsuccinyl.	Postshock	Pretreatment	Post-Thiopental	Postsuccinyl.	Postshock	Comment
Nodal	..	6	..	..	3	1	3	22	0	9	0	20	Post-thiopental, postsuccinylcholine, and postshock negative
V. P. C.*	2	4	1	..	6	..	2	14	3	7	3	18	Abnormalities in addition to those seen in previous column
Bigeminy	..	..	..	..	1	..	..	1	..	..	..	1	
A. P. C.†	..	2	..	2	1	1	1	3	2	3	..	5	
Bundle-branch block, interventricular and A. V. blocks	..	..	..	..	..	..	..	4	2	..	..	1	
Marked rate variation	..	5	..	1	1	..	1	5	..	..	..	10	
Sinus bradycardia	..	..	..	1	..	..	..	8	..	..	..	11	

* Ventricular premature contractions.
† Auricular premature contractions.

ment period also had some physical evidence of cardiovascular disease. The postconvulsive cardiac arrhythmias consisted of sinus arrests with nodal rhythms, ventricular premature contractions, and marked variation in rate with bradycardia. (Bradycardia is defined as a rate under 60 a minute; tachycardia, as a rate of 120 a minute or over.) It was noted that some of the patients in all four groups developed severe bradycardias; one patient had a transient rate of 17 per minute (Chart 1). Other types of arrhythmias, such as auricular premature contractions and bundle-branch, auriculoventricular, and interventricular blocks, were occasionally recorded. The types of arrhythmias did not appear to be influenced by the hypnotic and muscle-relaxant drugs; only the incidence.

Since these types of arrhythmias may be of vagal origin, we set up the sixth group, of 16, patients, in whom we varied the amounts of preanesthetic atropine. The amount of thiopental sodium, succinylcholine chloride, and electroshock current was not altered in any single patient. Although this group is a small sampling, the

postshock arrhythmias were decreased to less than half by the use of 1.5 mg. of atropine (56%, in control, to 25% in the 1.5 mg. atropine group). Not only was the incidence of arrhythmias decreased, but the duration was altered, most of these con-

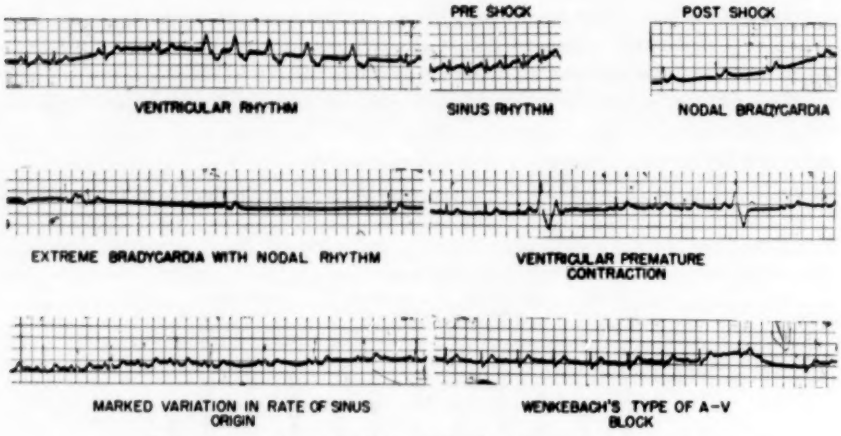

Chart 1.—Cardiac arrhythmias following electroshock therapy.

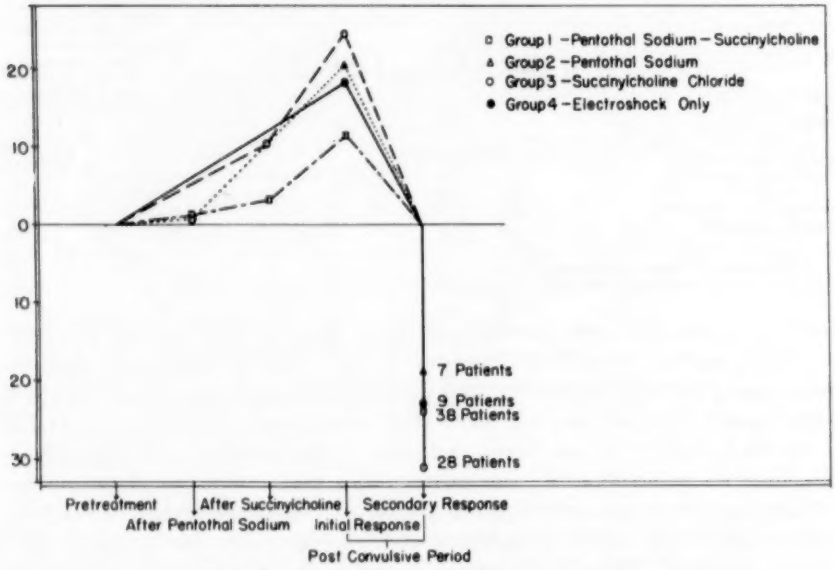

Chart 2.—Pulse changes from pretreatment values.

sisting of a single premature ventricular contraction. The bradycardias, nodal rhythms, and sinus arrests were abolished.

In regard to the effect of these agents on pulse rate, we noted no significant change after thiopental sodium, while a slight increase occurred after succinylcholine

chloride. There was less change when succylcholine chloride followed thiopental sodium than when succinylcholine chloride was given alone. It was felt that the discomfort of the muscle fibrillations and the fear associated with inability to breathe were partially responsible for this change. As noted in Chart 2, rather marked pulse rate changes occurred after electroshock. These were initially in the upward direction in all four series (maximum 85). However, only an occasional patient developed a rate of 120 or over. Certain patients in all four groups were then noted to develop a bradycardia (maximum decrease 100). As mentioned previously, the latter changes could be prevented by rather large doses of atropine.

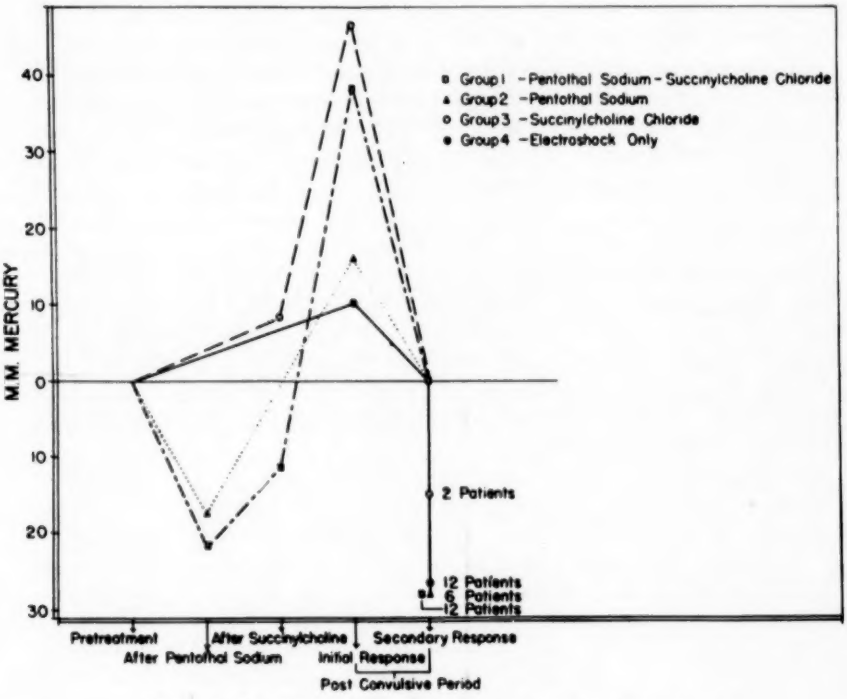

Chart 3.—Systolic blood pressure changes from pretreatment values.

Chart 3 indicates the mean change in blood pressure from control values. In groups I and II the systolic blood pressure decreased after thiopental sodium. The maximum decrease was 57 points. After succinylcholine chloride, an increase was noted in the systolic blood pressure in Groups 1 and III although the average blood pressure was still below control values in Group I. In the postconvulsive period marked increases in blood pressure were noted in all groups. This change was more marked in Groups I and III and was followed occasionally by marked hypotension (maximum 75-point decrease below control values). The average decrease below control values was 10 points for Group I and 18 points for Group III, with the other two groups showing a negligible average change below pretreatment values. However, if

only those patients are considered who had a secondary fall in blood pressure, it will be noted that Groups I, II, and IV had a similar average decrease. Of Group III, only two showed this hypotensive response. This hypotension was associated frequently with a marked bradycardia and/or nodal rhythm and, in Group VI patients, was prevented by 1.5 mg. of atropine. The diastolic blood pressure in general paralleled the systolic, although after administration of succinylcholine an equivocal decrease in pulse pressure was noted.

In Group V, 13 patients were treated with the four methods (electroshock alone; thiopental sodium-electroshock; succinylcholine chloride-electroshock; thiopental sodium-succinylcholine chloride-electroshock), with electrocardiographic and blood pressure recordings. The changes noted previously of statistical significance were again observed here in individual patients.

Ten patients were treated with thiopental sodium and tubocurarine chloride and observed in like manner. The cardiovascular response to curare differed from that of succinylcholine in that the hypotension following administration of thiopental was further accentuated by curare. The number of patients in this group is too small for statistical comparison of cardiac arrhythmias.

COMMENT

Electrocardiographic abnormalities have been noted previously after electroshock without specific drug therapy.[6] Arrhythmias were likewise noted in this series. The incidence of arrhythmias was increased with the employment of thiopental sodium and succinylcholine chloride; the increase, however, appeared to be associated primarily with the succinylcholine chloride rather than with the pentothal sodium. That is, pretreatment with succinylcholine appeared to be related to an increased incidence of postshock cardiac arrhythmias.

The addition of thiopental sodium to succinylcholine chloride appeared to reduce the incidence of arrhythmias following electroshock. Since thiopental sodium is generally regarded as vagotonic rather than vagolytic, this change is difficult of interpretation. Fright and discomfort related to the use of succinylcholine chloride alone appeared to be prevented by thiopental sodium, so that the differences noted in incidence of arrhythmias may partially be explained on this basis. However, arrhythmias were less common when thiopental was used alone than when used in combination with succinylcholine. Thiopental did not reduce the incidence of arrhythmias below that of those patients receiving no drugs. This implies some primary effect of succinylcholine on the control mechanism of cardiac rhythm. To confuse the picture, only a slightly increased incidence of arrhythmias was noted after succinylcholine in the preshock period. Although an attempt was made to eliminate extraneous factors, it is obvious that conditions were radically different in the postshock period among the various groups tested.

Patients having unmodified electroshock with a major convulsion pass through a short period of intense generalized muscle activity. The latter, by interfering with adequate respiratory gaseous exchange and increasing oxygen requirements, is often associated with intense cyanosis. Artificial ventilation during the convulsion is usually impossible. By contrast, the patients treated with this muscle relaxant, though often apneic, are readily ventilated with oxygen. Skin color remains excellent.

It should be reemphasized here that these arrhythmias were all transient in nature, usually of a duration of less than three minutes, and were of the same type as those seen after electroshock without drug therapy. In addition, both the incidence and the duration of arrhythmias were markedly reduced by adequate pretreatment atropinization. In fact, those patients treated with 1.5 mg. of atropine, thiopental sodium, and succinylcholine chloride had the lowest incidence of arrhythmias.

Thiopental sodium in this series produced no consistent change in pulse rate prior to electroshock. After electroshock these patients showed a transient tachycardia. Succinylcholine chloride was followed by a mild increase in rate, which was more marked when thiopental sodium was not utilized. After electroshock a transient tachycardia, followed frequently by a bradycardia, was noted. The bradycardia could be prevented by full atropinization.

Systolic blood pressure usually decreased after thiopental sodium. In many cases this decrease was quite marked. This change has been reported previously by Stephen and co-workers.[13] We noted that if thiopental sodium was administered slowly, this blood pressure fall was less marked. After succinylcholine chloride the blood pressure increased. In the patients who had received thiopental this increase did not compensate completely for the decrease following the thiopental sodium. In contrast, tubocurarine tended to accentuate this relative hypotension.

After electroshock, patients who had received succinylcholine chloride developed a sharp rise in blood pressure. This relative hypertension was associated usually with the aforementioned tachycardia. The increase of pressure was noted in all groups but was more marked in those treated with succinylcholine chloride. This rise was transient and was followed by a fall in blood pressure, which then often went below control values and was frequently associated with a bradycardia. The hypotension, as well as the bradycardia, usually could be prevented by full atropinization.

Hypertension and tachycardia represented to us a sympathetic nervous system response to electroshock. Patients who did not develop this hypertension also did not have tachycardia. This response probably represented a parasympathetic reaction. This differentiation in autonomic manifestations to electroshock has been previously reported by Wilkinson.[14]

The evidence suggests the following mechanism: Electroshock induces in some patients a relative increase in blood pressure and heart rate. This stimulates the aortic and carotid depressor mechanisms (vagal pathway), resulting in hypotension, bradycardia, and cardiac arrhythmias.

SUMMARY

Electrocardiographic tracings and blood pressure recordings were taken on 215 patients undergoing electroshock therapy.

Electrocardiographic arrhythmias were revealed by 2.6 to 8.7% of patients prior to treatment. Electroshock without drug therapy was followed by cardiac arrhythmias in 32.5% of patients; moderate tachycardia was initially induced, to be supplanted by bradycardia. Nodal rhythms, sinus tachycardias, and ventricular extrasystoles were the commonest arrhythmias observed. The systolic blood pressure increased sharply immediately after the electroshock and was associated with the tachycardia; patients who developed a bradycardia frequently had an associated

decrease in blood pressure below control values. These secondary changes appear to be a function of the aortic depressor reflex.

Thiopental (Pentothal) sodium induced a transient hypotension with little effect on pulse rate, although 16.1 to 17.5% of patients developed arrhythmias. After electroshock the blood pressure and pulse rate were transiently elevated, to be replaced at times with bradycardia and hypotension; 34.2% of patients had abnormal cardiac rhythms.

Succinylcholine chloride administration appeared to induce a mild increase in pulse rate and systolic and diastolic blood pressure. An incidence of 10.5 to 21.5% of cardiac arrhythmias was recorded. After electroshock a fairly marked rise in blood pressure and pulse rate occurred. This was followed in some patients by a marked fall in blood pressure associated with a bradycardia. An increased incidence of postshock cardiac arrhythmias was recorded in the patients treated with succinylcholine. Pretreatment with thiopental, and particularly with adequate amounts of atropine, reduced this incidence below that of patients receiving no drugs. On this basis, it is concluded that most of these arrhythmias are of vagal origin.

Since adequate pretreatment atropinization largely prevented postshock reflex bradycardia, hypotension, and abnormal cardiac rhythms, this measure is recommended. While we formerly prescribed 0.4 to 0.6 mg., twice that amount appears to be required for adequate prophylaxis.

Blood oxygenation and circulation, as noted by skin and fingernail color and capillary-refill time, remained excellent in all patients treated with thiopental sodium and succinylcholine chloride. This is in contrast to the condition in patients treated with unmodified electroshock, who frequently show a very intense cyanosis. In the entire series of patients treated with succinylcholine chloride, detrimental effects on cardiac status were not observed in any patient after treatment. The mortality rate was zero.

We feel very strongly that physicians using hypnotic and muscle-relaxant drugs should have adequate knowledge of the principles of resuscitation. Cooperation between the members of the psychiatric and the anesthetic departments is of benefit to the patient.

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ELECTRIC SHOCK TREATMENT AND THE MENSTRUAL CYCLE

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DISTURBANCES in the menstrual cycle are frequent concomitants of electric shock therapy. Since menstruation is an outward manifestation of endocrine function intricately related to the sensitive balance of the hypothalamic and pituitary coordinators, the disturbance in menstruation was deemed worthy of search for possible clues to the mechanisms of electric shock treatment.

METHODS

The records of 687 female inpatients of the New York State Psychiatric Institute treated during the years 1942 to 1949 were reviewed for data pertinent to the study. Criteria for selection of cases were (1) at least one menstruation in the hospital before electroconvulsive therapy (ECT) was begun; (2) a sufficient length of stay in the hospital after ECT for the occurrence of postshock menstruation or the establishment of amenorrhea.

The clinical and experimental nature of the material led to considerable variability of the pattern of shock treatment. In a sizable proportion of patients ECT was combined simultaneously or in succession with coma or subcoma insulin treatment. Many patients were begun on ECT soon after admission before the occurrence of their first hospital menses. This factor disqualified the greatest number of records of the study.

Mental illness itself may lead to menstrual disturbance, especially amenorrhea.[1] In a representative sample of 278 patients treated in the years 1942 to 1944, inclusive, 26 patients between the ages of 15 to 45 failed to menstruate prior to treatment even though they had been in the hospital in excess of 60 days. By comparison, 128 patients of this same sample menstruated. Of these 43 had been in the hospital in excess of 60 days prior to treatment. Thus the incidence of amenorrhea of at least 60 days' duration in this representative sample may be estimated at approximately 38% ($\frac{26}{26+43} \times 100$). It may be assumed that the same proportions applied to the patients who were in the hospital less than 60 days and that, given adequate time, a greater number would have menstruated than the actual recorded number of 128 of 278.

Patients were frequently discharged before postshock reappearance of menses. Since protracted amenorrhea was a common consequence of ECT, it was deemed incorrect to omit these patients from the calculations. Exclusion of patients with

From the clinical services of the New York State Psychiatric Institute, New York, and The Institute of Living, Hartford, Conn. Dr. R. C. Robertiello, former resident of the New York State Psychiatric Institute, assisted in the preliminary phase of this study.

amenorrhea would lead to weighting of the data in favor of those who were included in the study by virtue of menstruating early. Therefore, patients who were discharged 30 days or more after a previous menstrual bleeding or later than 30 days after the last treatment were included in pertinent studies, and the discharge dates were substituted for dates of menstruation.

RESULTS

Of the total 687 records reviewed, 331 had sufficient data for the study. Individual subjects lacked part of the data but qualified for specific aspects of the investigation. The number of subjects therefore varies in subgroup studies.

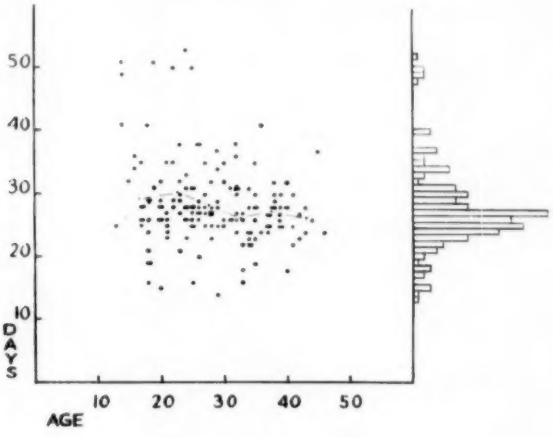

Chart 1.—Scatter diagram and frequency distribution of menstrual cycles, in days (left ordinate), correlated with age (abscissa) in 159 mental patients who subsequently received ECT. Crosses connected by lines indicate averages of age groups.

One hundred fifty-nine patients menstruated at least twice in the hospital before being treated by electric shock, thus providing a complete cycle as a control. The average length of cycle of these mentally ill women was 28.51 days. The variability in length of cycles was greater in the younger patients. The average length of cycle was longer in the younger patients, averaging 29.8 days in the 13 to 20 age group, as contrasted to 26.6 days in the 41 to 46 age group. Statistically the correlation of the length of the menstrual cycle with age was a negative one, extremely low ($r = -0.21$) and of doubtful significance (standard error = 0.05). The distribution and correlation with age are represented in Chart 1.

Postponement of menstruation — amenorrhea — was one of the conspicuous changes following shock treatment. Occasionally amenorrhea persisted as long as

treatments were continued and for variable intervals after the end of treatment. Thus, one patient who received a total of 54 treatments over a period of 8½ months failed to menstruate for 268 days.

After ECT the distribution of menstrual intervals shifted in the direction both of longer and of shorter intervals. Shock treatment evidently led both to shortening

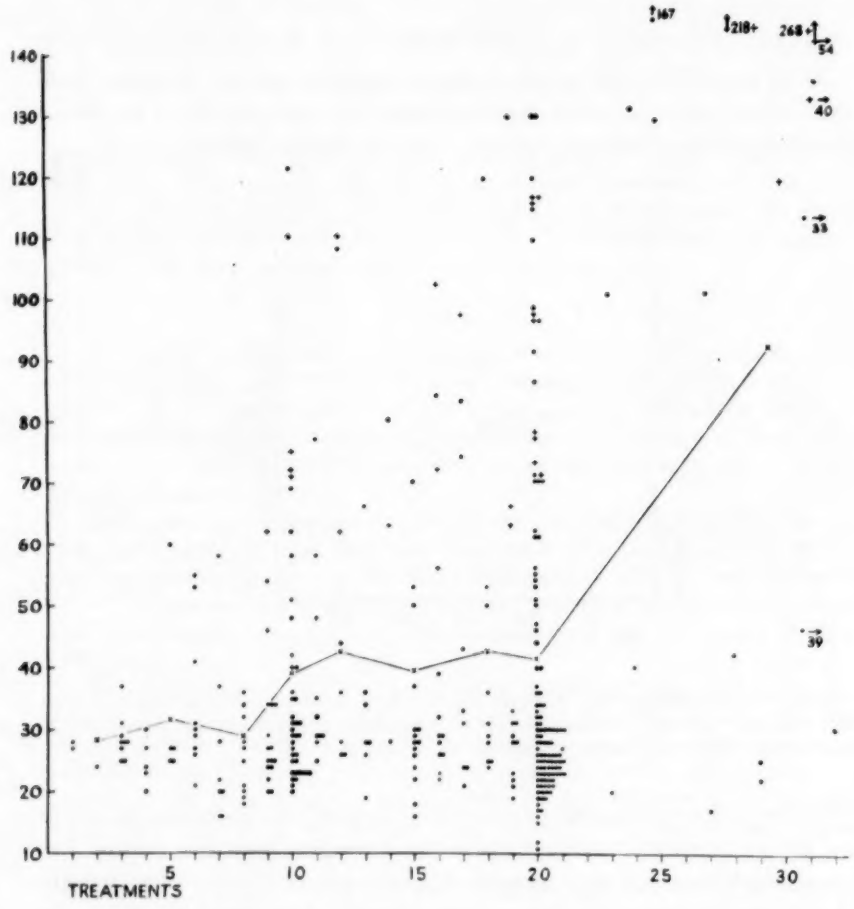

Chart 2.—Effect of ECT on the current menstrual cycle in 331 patients. Length of cycle, in days, is indicated on left ordinate; number of treatments on abscissa. Crosses indicate discharge dates for patients who did not menstruate within 30 days from last menses. X's connected by line indicate averages of patients grouped by three treatments except for groups receiving 10, 20, and over 20 treatments.

and to lengthening of the menstrual interval (Chart 2). As a consequence of the diversity of response to shock therapy, the average length of the menstrual cycle was influenced only slightly until at least 10 treatments were given (Chart 2). With 10 treatments, and up to 20 treatments, the average length of the first treatment

cycle remained at approximately 40 days. It increased conspicuously thereafter to 91.6 days in 19 patients, who had an average of 29.5 treatments. The average—31.86 days—for the menstrual cycles of a group of 58 patients who received from 1 to 9 treatments differed significantly from the average of 39.95 days for a group of 241 patients receiving 10 to 20 treatments ($t = 3.52$). Since 68% of the former group and 80% of the latter group menstruated while ECT was still in progress, the difference in the two groups was probably codetermined by factors other than the eventual total number of electric shock treatments.

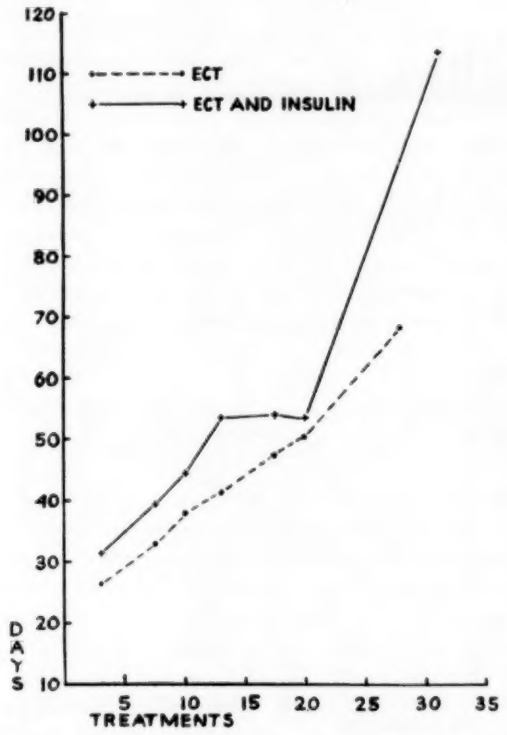

Chart 3.—The length of average menstrual cycles, in days (left ordinate), increases with increasing numbers of treatments (abscissa).

Without insulin: $N = 199$; $r = 0.34 \pm 0.042$.
With insulin: $N = 128$; $r = 0.58 \pm 0.040$.

In most patients the period of shock treatment extended into a second menstrual cycle, and occasionally even three menstrual cycles coincided, at least in part, with shock treatment. Chart 3 represents the average lengths of menstrual cycles throughout the duration of treatment in correlation with the number of treatments given. The average length for individual patients was derived by dividing the number of days from the first day of menstruation immediately preceding the shock treatment to the menstruation immediately following shock treatment by the number of

menstrual cycles occurring in this interval. The average length of the menstrual cycle was correlated with the number of electric shock treatments. The correlation coefficient (r) between these two variables in 199 patients was 0.34, the probable error (P. E.), 0.042.

The average menstrual cycles were longer and the correlation coefficient even more significant in 128 subjects in whom ECT was combined with subcoma or coma insulin ($r = 0.58$; P. E. $= 0.040$; Chart 3).

Return of menses after completion of shock treatment was not definitely related either to time elapsed from a previous occurrence of menstruation or to the termina-

Chart 4.—Distribution of subjects (left ordinate) according to intervals, in days (abscissa), between last shock treatment and recurrence of menses.

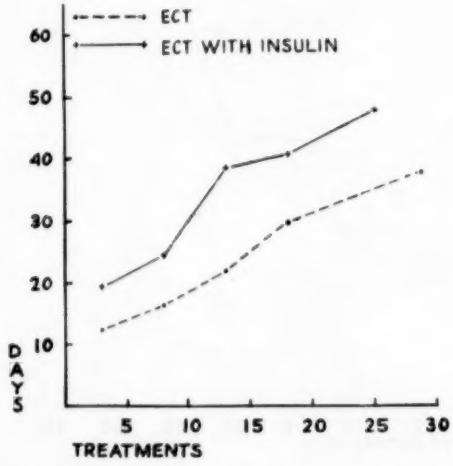

Chart 5.—Return of menses after last treatment is delayed proportionately with increasing numbers of treatments.

Without insulin: $N = 103$; $r = 0.29 \pm 0.061$.
With insulin $N = 106$; $r = 0.38 \pm 0.056$.

tion of shock treatment. But the distribution of the time elapsed between cessation of treatment and the recurrence of menses did form a low peak at the approximate length of one menstrual cycle, e. g., 24 to 30 days (Chart 4). There was also a moderate aggregation at the seven- to eight-day interval. Thirty-two patients who were discharged 30 days or more after completion of treatment and failed to menstruate while still in the hospital are not included in Chart 4. The data in Chart 4 are therefore unduly weighted in favor of patients who menstruated early.

The return of menses after ECT bore direct relationship to the number of treatments given. The more extensive the course of treatments, the longer the period of amenorrhea after ECT (Chart 5). It might be said that the individual shock treatments of a course of treatment added up to a cumulative effect, which lasted longer if more treatments were given.

The correlation between the number of treatments and the length of interval to return to menses was of low order and only marginally significant for 103 subjects receiving electric shock alone ($r = 0.29$; P. E. $= 0.061$). A higher and more significant correlation was obtained for 106 subjects in whom ECT was combined with insulin treatment ($r = 0.38$; P. E. $= 0.056$).

The menstrual cycles during shock treatment could be classified into a variety of patterns, depending on the lengths of intervals. The most frequent pattern was complete absence of menstruation throughout the duration of shock treatment. Of 150 patients whose treatment was of sufficient length to enable the occurrence of two menstrual cycles during treatment, 34 did not menstruate at all while under treatment. The next most frequent pattern was a shortening of the first cycle to 24 days or less, with a following long cycle of more than 30 days, which occurred in 27 subjects. To this group might be added a group of seven whose first cycle was short, followed by a cycle of average length of 25 to 30 days. Twenty-five subjects menstruated within an average time (25 to 30 days) and went on to develop prolonged amenorrhea; an additional 17 subjects showed lengthening of both the first and the second menstrual interval. Only 14 subjects menstruated within 25 to 30 days in both consecutive cycles.

In general the second cycle during shock treatment tended to be longer than the first cycle. Only 26 subjects of the total of 150 had a second cycle shorter than the first.

Patients became amenorrheic due to shock treatment, but the reverse was also true. Patients who were amenorrheic in conjunction with emotional illness resumed menstruation during or after a course of shock treatment. Thus, 8 of the 26 patients cited above under "Methods" with amenorrhea of more than 60 days' duration recovered menstruation after a course of ECT.

Combination of ECT with insulin therapy enhanced the menstrual changes in the direction of amenorrhea. The average length of intervals from the last shock treatment to the reappearance of menses in 103 patients, who received an average of 14.99 electric shock treatments, was 26.32 ± 19.00 days. This same average in 106 patients on combined coma or subcoma insulin treatment, who by coincidence also received an average of 14.99 ECT's, was 36.36 ± 24.03. The difference between the means is statistically significant at the 0.01 probability level ($t = 3.36$).

INTERPRETATION

The variability of responsiveness from one patient to another and the wide range of menstrual irregularities make physiological interpretations of the effect of ECT on the menses difficult and at best speculative. Even the site of action of shock treatment is subject to dispute. It is generally accepted that neither the uterus nor the ovary is substantially influenced in terms of menstruation by impulses coming to them by way of the nervous system. Nevertheless, precipitous menstruation had

been observed after abdominal operations in patients who were previously amenorrheic for extended intervals.[3] Stimuli arising in the central nervous system from shock treatment might conceivably alter the regularity of the menstrual cycle.

On the other hand, the concept that the various phases of the menstrual cycle are controlled from the pituitary gland via the ovary is well documented.* Animal experiments and clinical observation point to the pituitary as the site of action of shock treatment. Thus, for instance, pregnancy in white rats is not maintained if shock treatments are applied early after insemination.[4] Pregnancy is maintained, however, if shock treatments are started after a lapse of at least 48 hours after insemination. At least five treatments must be given.[5] Shock treatment does not lead to interruption of clinically established pregnancy in the human expectant mother. These observations support the concept that once a luteal-decidual hormone relationship is established and the pituitary no longer relied upon as a source of gonadotropic hormones, electric shock no longer interferes with gestation.

Not until the pituitary is once again called into action at the time of parturition and lactation does electric shock disturb the natural course of gestation, by interfering with labor and maternal behavior.[6] The pituitary glands of the shocked animals showed histological changes and the corpura lutea were small.[5]

The animal experiments indicate suppression of pituitary function. Theoretically, suppression of gonadotropic functions of the pituitary may cause prolonged amenorrhea. This is accomplished in terms of Reifenstein's concept of hypothalamic amenorrhea,[2] in which it is postulated that luteinizing hormone (LH) fails to evolve, owing to emotional hypothalamic disturbance. This, in turn, leads to lack of production of estrogenic hormone, since follicle-stimulating hormone is without effect if no traces of LH are available.[7] This mechanism would further lead to lack of development of the uterine mucosa and to amenorrhea.

Termination of shock treatment should lift the hormone-suppressing mechanisms. A resurgence of ovary-stimulating hormones should lead to resumption of the cyclic hormonal functions and to resumption of menstruation. The starting point in the cycle should be the time of release from the suppressing activity of shock treatment. Menstruation should occur approximately one menstrual interval distant from the starting point. The actual data support these theoretical deductions to some extent. The distribution of intervals of return of menses forms a peak at the 24- to 30-day interval. The peak of distribution at the interval of approximately one menstrual cycle might be interpreted as due to accumulation of cases in which hormone-suppressing activity was released on termination of shock treatment.

Sudden withdrawal of hormonal support from the uterine mucosa at a time when it is fully evolved leads not to amenorrhea but, rather, to precipitous bleeding. Withdrawal of therapeutically administered progesterone leads to bleeding within 24 to 72 hours, while withdrawal of regularly administered estrogen leads to bleeding in 6 to 10 days. It is therefore not surprising to find a number of subjects who menstruated within a few days after their first shock when therapy was begun during the presumed luteal phase of the menstrual cycle. These are the patients whose first cycle during shock treatment was shortened. The first shock cycle of

* References 7 and 8.

42 of a representative group of 150 patients was 24 days or shorter in duration. Not only decreased production of follicle-stimulating hormone (FSH) but also increase of the same hormone may lead to amenorrhea on the theory † that increase in FSH leads to hyperfolliculization of the ovary. Excess of estrogen, in turn, leads to suppression of LH and failure of ovulation and corpus luteum formation with consequent amenorrhea. This is presumed to be a mechanism of amenorrhea in the early stages of the menopause.[8]

Amenorrhea may thus be an end-product of excess estrogen production as well as the result of lack of estrogen. Evidence in favor of the former type of amenorrhea might be seen in the secondary peak of distribution of recurrence of menses after shock treatment at the seventh-eighth day interval. This peak might be interpreted as corresponding to the bleeding which occurs after withdrawal of estrogen in the therapy of amenorrhea, or to the metrorrhagia occurring in the early stages of the menopause.

As may be seen on Chart 5, the accumulation of patients in the two peaks is by no means conspicuous or overwhelmingly significant. The distribution of return of menses is spread out quite evenly throughout the range up to approximately 40 days with only slight aggregation around the seventh and eighth day and again at the interval of approximately one menstrual cycle. The peaks of distribution might even be considered insignificant; however, they are enhanced by grouping in classes, for instance by three days, and thus confirm the consistency of the pattern. Since physiological interpretations may be found for the peaks of distribution, it seems reasonable to assume that they are not a chance phenomenon but are, rather, a true manifestation of the effect of shock treatment.

The peak at the seventh-eighth day interval is represented by a very few patients. The incidence of estrogen-stimulating function must therefore be exceptional, in contrast to inhibitory activity, which is probably the prevalent mode of action of electroconvulsive therapy in patients who menstruate.

The broad distribution of the intervals of return of menses indicates that not all patients react to the inhibitory or excitatory effect of shock treatment with equal sensitivity. This contention is further supported by the low correlation between the total number of treatments and the interval of return of menses after shock treatment. The low significance in both these statistical estimates of correlation can be interpreted as indicating that shock treatment cannot completely dominate the endocrinological mechanisms to an equal degree in all patients, nor can it, in fact, reach all patients.

The effect of shock treatment on menstruation was studied on a preselected group. Only patients who menstruated were included in the study. Their menstrual physiology was so strong that it was not deranged by mental illness. If a statement is made that the evidence from the data points to a prevalence of suppression of pituitary gonadotropic function by shock treatment, it applies only to the approximate 62% of patients who menstruated. It is possible that the mechanism of shock treatment was quite different in the 38% of patients in whom the menstrual function was weak or absent at the outset of treatment.

† Lewin and Spiegelhoff,[8] p. 196.

The interpretation that both decrease or increase in pituitary gonadotropic function may occur after ECT is in conformity with a related finding in the sex function in the male, in whom both development of impotence [9] and recovery from impotence may be observed after ECT. Increase or decrease in endocrine function was also inferred in the thyroid [10] and the adrenal cortex.[11] The possibility must also be considered that both decrease and increase in gonadotropic function might occur in the same individual in sequence—a course which under normal conditions is part of the physiology of the pituitary-ovarian axis.

From the clinical point of view, adequate and lasting therapeutic effect requires almost without exception a multiple series of treatments. The disturbances in menstruation parallel to some extent the clinical observation. The greater the number of treatments, the more extensive and enduring is the amenorrhea. It is tempting to speculate that perhaps the mechanism which underlies clinical improvement might have at some juncture a denominator common to the menstrual disturbances.

In conclusion, it might be said that the evidence from observations on the menstrual cycle points to substantial influence of ECT on the endocrine system. Shock treatment evidently wields its influence at the pituitary-hypothalamic level, where it either suppresses or increases pituitary function.

This conclusion is based on evaluation of menstrual changes—a measure of change in hormone level which is not accredited with the same reliability as hormonal assays on animals. The evidence is nevertheless suggestive and directs attention to the need for confirmation by better controlled laboratory measures—the animal assay or biochemical estimate.

SUMMARY AND CONCLUSIONS

Introduction of electroconvulsive therapy into a menstrual cycle either shortened the menstrual cycle or unduly lengthened the cycle, thus causing temporary amenorrhea.

The averages of the first cycle during shock treatment increased but little up to the 10th treatment, when a sudden rise to a higher level occurred.

The averages of all menstrual cycles during ECT were significantly related to the number of treatments given.

The effect of a series of shock treatments was cumulative. Increasing numbers of shock treatments caused increasing delay in resumption of menstruation after treatment.

The amenorrhea-producing properties of ECT were enhanced by combined subcoma or coma insulin treatment.

The data were interpreted as indicating that either diminution or increase of pituitary gonadotropic function may occur during ECT, the prevalent mode of action being diminution.

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METABOLIC AND ELECTROENCEPHALOGRAPHIC CHANGES IN IDIOPATHIC EPILEPSY

A Detailed Case Study

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THE STUDY to be described was carried out to determine the effect of cortisone in a case of idiopathic epilepsy. McQuarrie and associates [1] had previously demonstrated that desoxycorticosterone reduced the number and severity of seizures provoked by a vasopressin hydration regimen. Aird and Gordon [2] also showed that desoxycorticosterone reduces the severity and frequency of seizures in epileptics on no other treatment and referred to the drug as an anticonvulsant. Both Aird and Gordon [2] and Klein and Livingstone [3] also found that desoxycorticosterone reduced electroencephalographic abnormalities in epileptics. Because of the similarity of desoxycorticosterone and cortisone in structure and in certain metabolic actions, it was thought that cortisone might be similarly anticonvulsant.

The decision first had to be made whether to conduct limited observations on a group of epileptics or whether to study one patient intensively. The latter plan was followed. The patient chosen had severe epilepsy, was available for long-term hospital study, and was considered to be a suitable subject psychologically. He was observed in the hospital for three periods of a month each over a six-month interval. The first week or so was used as a control period, during which time studies were begun, first, by establishing a normally balanced diet. An accurate knowledge of the dietary intake was essential because of the known influence of the steroids on electrolyte and water metabolism.* Detailed observations were made on the dietary sodium, potassium, chlorine, nitrogen † and fluid intake, including the preformed water and the water of oxidation of food. Intake studies were compared with the urinary output of sodium,‡ potassium,‡ chlorine,[11] nitrogen,[12] cortisone,[13] and 17-ketosteroids.[14] In addition, determinations were made on fasting blood for the eosinophile count,[15] the serum sodium,‡ potassium, and chlorides,[16] and the carbon dioxide-combining power.[17] Electroencephalograms were recorded at appropriate intervals during the investigation *post cibum* to avoid hypoglycemia.

From the Department of Medicine and Physiology, University of Alberta.

Read at the Fourth Annual meeting of the Canadian Neurological Society, Banff, Alta., Canada, June 8, 1952.

* References 4 and 5.

† References 6 through 8.

‡ References 9 and 10.

REPORT OF CASE

Mr. M. A., aged 49, gave a history of convulsions at the age of 1½ years, after which he remained well until the age of 24. At that time he was thrown from a horse. After this episode he recovered and remained well for six years. He then had his first epileptic seizure. Two similar attacks occurred during the ensuing year, and gradually throughout the next seven years their frequency increased. The seizures occurred at regular intervals of 10 days, when he would have four or five seizures on a single day, after which he would be seizure-free for another 10 days. This pattern continued until four years prior to the present admission, at which time treatment with diphenylhydantoin (Dilantin) was started. He was then 45 years of age. Under this treatment the attacks became progressively less frequent over a period of seven months. He was then seizure-free for 11 months, after which his attacks again returned, four to five times a day at two-week intervals, and to date this cycle has persisted in spite of treatment.

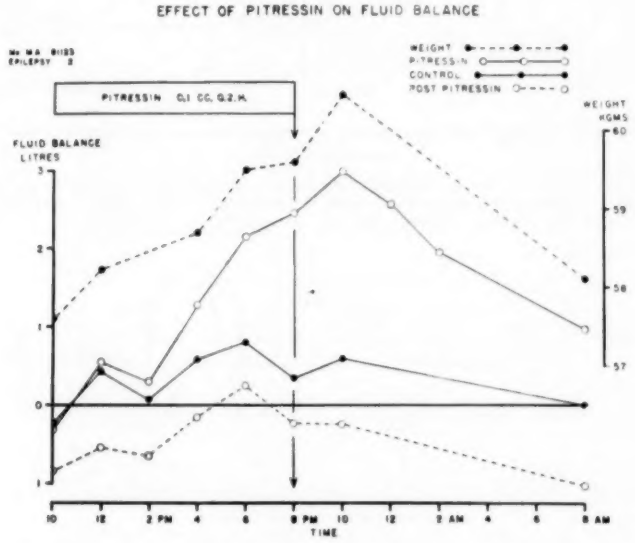

Fig. 1.—Effect of vasopressin injection U.S.P. (Pitressin) on fluid balance. Cumulative water balance calculated at two-hour intervals as compared with a control curve shows a retention of water, paralleled by a weight gain of similar magnitude following the administration of vasopressin. Water diuresis occurred with discontinuation of the drug.

A typical attack is as follows: The onset is usually preceded for 12 to 24 hours by a frontal headache. The aura varies, but usually consists of a sense of constriction in either his chest or his "stomach," followed by pain at the back of his head and a burning sensation at the root of his nose. Often he grasps his nose with his left hand before losing consciousness. His head, eyes, and the corner of his mouth have been reported to move to the right during a severe seizure. The convulsions are generalized and last about three minutes. Formerly he lost control of bowel and bladder sphincters. There is postictal depression, characterized by severe headache of 2 to 3 hours' duration and profound weakness for 24 hours. There is no localized postictal weakness or paralysis.

On physical examination the patient was at first suspicious and moderately paranoid but soon became very cooperative. The general physical examination disclosed no significant abnormalities. Detailed neurological examination also revealed no abnormalities of significance in spite of a history of head injury at the age of 24. A suggestion of hyperactivity of all reflexes was noted, which, however, was consistent with the tense nature of the patient.

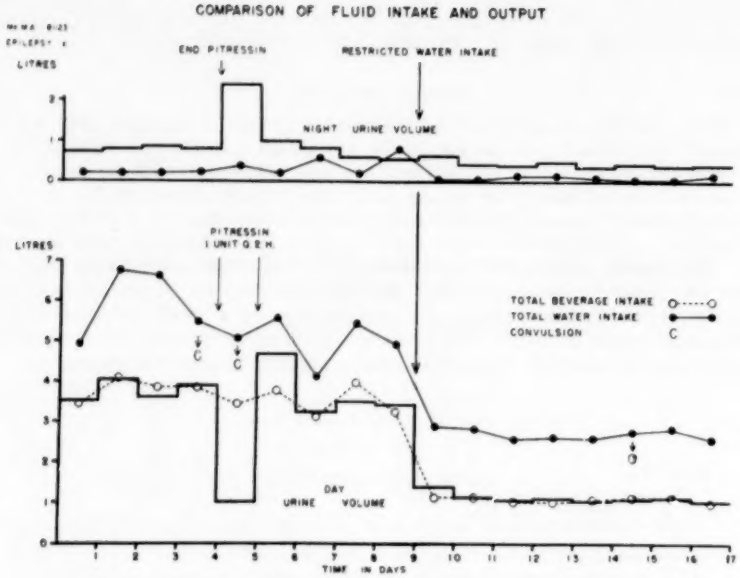

Fig. 2.—Effect of reduced water intake and vasopressin (Pitressin) on fluid balance. Vasopressin therapy resulted in diminished urine output. Similarly, restricted water intake reduced the day urine volumes to normal.

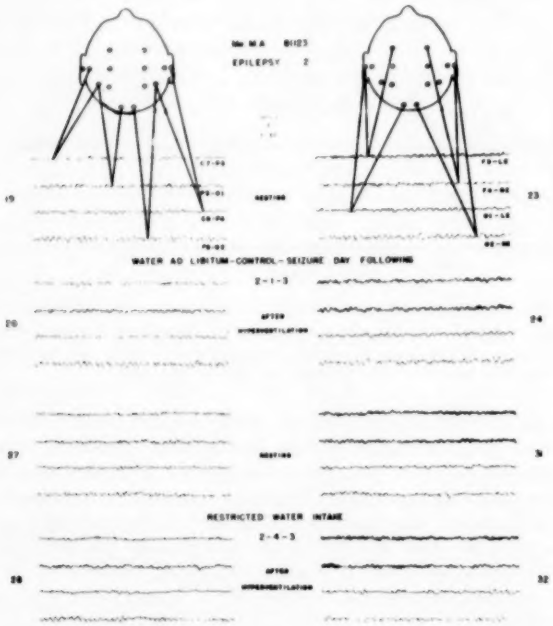

Fig. 3.—Effect of restricted water intake on the electroencephalogram. Note significant improvement following restriction of water intake. Delta wave voltage dropped from 80 to 40 μv, and fewer delta (4 per second) waves interrupted the normal alpha (10 per second) rhythm.

The blood, urine, and skull x-ray findings were normal. The electroencephalogram showed a moderate generalized slow-wave dysrhythmia, which was severest in the right posterior head region. Pneumoencephalographic studies done two years previously showed no abnormality.

The patient continued on his standard medication (diphenylhydantoin sodium, 1½ grains [0.10 gm.], and methylphenylethyl hydantoin [Mesantoin], 100 mg. t. i. d., p. c.) throughout the entire investigation to prevent the occurrence of status epilepticus or a change in the irritability of his central nervous system.

Clinically, we believe the patient has cryptogenic epilepsy, the only localizing signs being a doubtful right adversive movement with possible right facial twitching. The electrical abnormality, however, is more marked in the right posterior quadrant, but the dysrhythmia is diffuse, and true focal electrical abnormality is not evident.

The following results were obtained from three periods of study in the hospital.

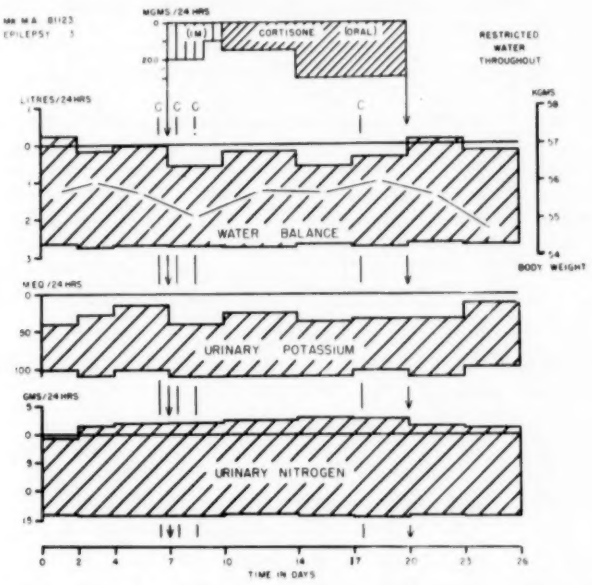

Fig. 4.—Metabolic data showing the effects of cortisone. Note retention of water and potassium but diuresis of nitrogen. Metabolic data on this Figure and on Figures 5 and 7 are arranged according to the scheme of Albright.[5] There is a horizontal base line; intake is charted on a reverse scale downward from the base line; the urinary excretion is then measured from the intake line upward toward the base line. If output exceeds intake, the final level will be above the base line. Thus, a positive balance will be indicated by a clear area above the base line; a negative balance, by a shaded area above the base line.

During the first six days of study the daily average urinary output of the patient was about 4 liters. This polyuria suggested the possibility of diabetes insipidus. It was decided, therefore, to continue observations with no change in therapy. For two weeks electrolyte balances could not be established for technical reasons. Water balance studies were, therefore, carried out, and the effects of vasopressin injection were observed. Vasopressin produced a marked retention of water, which resulted in a weight gain of approximately 1.2 kg. in 10 hours (2.1% of body weight).

This procedure was repeated during the second period in the hospital and was followed by more complete data on water balance (Fig. 1). A weight gain in 12 hours of 3 kg., or 2.3% of body weight, was observed. This corresponded to a measured positive water balance of 2.5 liters. He had a seizure at 10 hours on vasopressin therapy, and the electroencephalographic abnormality was exaggerated.

These data on water retention were not conclusive. The weight gain was rather rapid, and may have been explained by an inadequate production of endogenous antidiuretic hormone. Further, the control studies showed abnormally high water intake, and the patient at first insisted

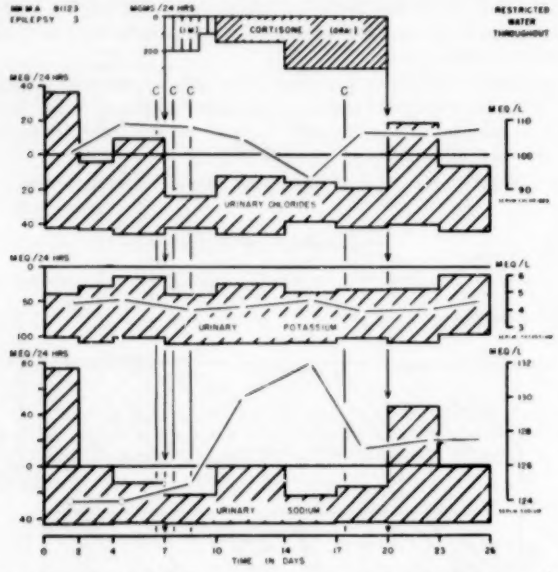

Fig. 5.—Data showing metabolic effects of cortisone on electrolyte balance. Note the retention of chlorides and of sodium.

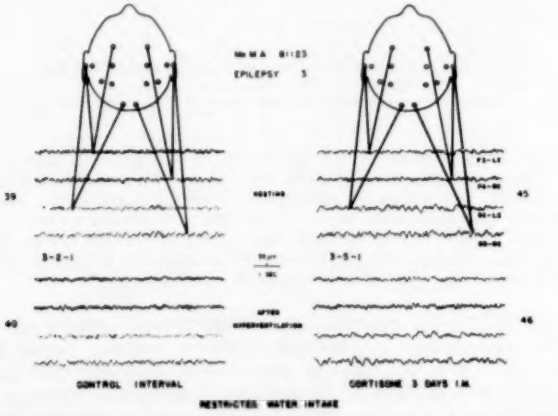

Fig. 6.—Electroencephalographic changes following the use of cortisone. Note the increase in abnormal electrical activity and the presence of more high voltage delta waves in the alpha rhythm.

that he could not tolerate a reduction of it. However, such a weight increase with vasopressin could possibly result solely from a high water intake habit, without concomitant endocrine deficiency. The patient was, therefore, placed on a restricted free-water intake of 1 liter, which was tolerated.

The results were interesting. The patient felt better. Daily urine volumes dropped from a mean of 4.5 liters to 1.5 liters (Fig. 2). There was also significant improvement in the electroencephalogram (Fig. 3). These responses were so definite that the patient was followed for nine days further in the hospital and discharged on his restricted water regimen.

Before vasopressin therapy the patient was having seizures similar to those described in the history approximately every two weeks. During therapy with vasopressin, he became progressively weaker as the water retention increased, with prompt improvement on cessation of the drug. After the reduction in fluid intake, the patient complained less frequently of weakness. He reported that he was able to go about his work shortly after a seizure, whereas formerly he was incapacitated for up to 24 hours after an attack. After his discharge he undertook to do very heavy work, and he noted that, although there was no alteration in the frequency of seizures, they were much less severe and the feeling of weakness was much reduced.

After one month of observation as an outpatient, he was readmitted for a third period of study. The low-water regimen was continued, and, after a control period of one week, cortisone was administered for 13 days. After cessation of therapy the patient was observed for a further six days.

In effect, the metabolic responses to cortisone were normal[18] (Figs. 4 and 5). There were retention of sodium, chlorides, and water; a slight diuresis of nitrogen; increased urinary output of corticoids and 17-ketosteroids, and a depression of the circulating eosinophile level.[19] Retention of potassium was noted. The clinical improvement since institution of the lower intake was not maintained during treatment with cortisone. The patient became slightly more paranoid, although at times he exhibited a greater sense of well-being than usual.

During treatment with cortisone there was a generalized increase in abnormal electrical activity, and high voltage delta waves (notably 4 per second, reaching 90 μv) were seen appearing more frequently in the alpha rhythm (Fig. 6). The abnormality was diffuse, but remained more localized in the right occipital region.

COMMENT

The interpretation of the results of electrolyte and water balance studies is, to say the least, confusing. From a review of the results obtained on this patient, it is evident that the common denominator associated with procedures which made the patient worse was water retention, and that which made him better was a loss of body water. This patient became worse both clinically and electrographically on vasopressin and cortisone therapy. With both there was water retention and a gain in weight. He improved on a restricted water intake.

The question arises whether changes in electrolytes were in themselves the explanation. The evidence is against this because the electrolyte balance did not vary in a manner consistent with the changes in the clinical and electrical manifestations. For example, there was a loss of sodium with vasopressin (Fig. 7) and a retention of that element with cortisone, but the patient was worse during both treatments. Further, while there was an unexplained retention of potassium during the whole period of observation, this was not significantly altered by the procedures which markedly affected the clinical state. Potassium would, therefore, seem unrelated to the argument, as has been suggested previously by Woodbury and associates.[20]

From recent work,[21] the actions of the adrenal hormones in epilepsy seem to have a definite bearing on epileptic activity. Desoxycorticosterone has been shown to improve the condition of the epileptic and to reduce the excitability of the central nervous system in animals.[20] In our study, cortisone was found to be detrimental. It has also been shown that the adrenals of epileptics are heavier and contain more cholesterol than those of normal subjects,[22] and that corticotropin restores the excitability of the central nervous system previously reduced by desoxycorticos-

terone, presumably by stimulating the production of the other adrenal hormones.[20] These facts give significance to the known effect of psychic stimuli or stress in precipitating seizures in epileptics. The evidence just cited [21] and our own results with cortisone are thus consistent. One might argue that stress should also stimulate endogenous desoxycorticosterone production, which would be expected to reduce the convulsive tendency. However, Greep and Deane [23] have suggested that the adrenal release of desoxycorticosterone does not result from corticotropin stimulation, whereas the androgen- and cortisone-like hormones are thus produced. This could explain the predominant release of cortisone-like substances in stress, which state is known adversely to affect the epileptic. Psychological and environmental influences and the physiological responses of epileptics are thereby related.

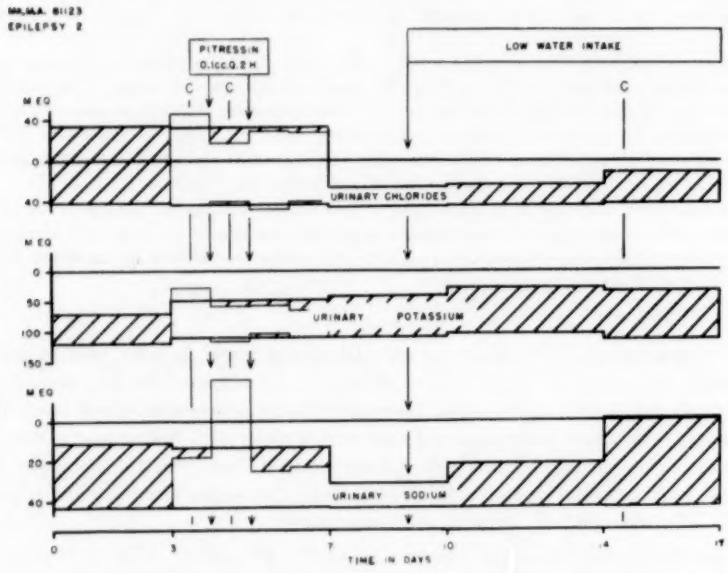

Fig. 7.—Metabolic data showing effects of reduced water intake and vasopressin (Pitressin) on electrolyte metabolism. Note particularly the loss of sodium during administration of vasopressin.

In spite of the evidence that the adrenal hormones do modify the epileptic state, the mechanism by which they do so is still not clear.

This study, however, emphasizes the importance of water itself. Water metabolism may be disturbed through the adrenal hormones or through water intake. It is thus possible to upset nervous irritability by a high water intake, as is well known§; on the other hand, even a normal intake may be detrimental in a patient in whom the adrenal hormone release is abnormal. The clinical significance of this is that water intake can be restricted. Possibly in the future greater knowledge of adrenal cortical activity may permit more rational application of hormone therapy to the epileptic.

§ References 24 and 25.

SUMMARY

Detailed observations were made for several months on an epileptic patient under an accurately controlled regimen. The severity of seizures was markedly reduced by a restricted fluid intake. There was also electroencephalographic improvement, though the frequency of seizures was unaltered. Throughout the observation potassium was inexplicably retained. Cortisone made the patient's condition worse. Results of further observations, e. g., corticoid and 17-ketosteroid outputs and electrolyte balances, were of no significance.

The clinical importance of water intake in the control of epilepsy is discussed.

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SERIAL ADMINISTRATION OF THE "AMYTAL TEST" FOR BRAIN DISEASE

Its Diagnostic and Prognostic Value

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A METHOD of using amobarbital sodium (Amytal Sodium) to study alterations in brain function has been described in previous papers. It has been noted that under the effect of this drug patterns of denial of illness [1] and disorientation for time, place, and person [2] could be reproduced in patients with brain disease after these phenomena were no longer present clinically.

In an effort to determine the value of amobarbital for diagnostic purposes a standardized procedure of interviewing was developed.[3] In comparing the changes in behavior under amobarbital sodium of a group of 88 patients with brain disease and 50 normal * control patients, it was found that the presence of certain patterns of denial of illness and disorientation could differentiate the two groups empirically. Altogether, 57, or 65%, of the patients with brain disease showed behavioral changes not found in any of the control group.

It was noted that the incidence of such "positive" reactions had a relationship to the type, location, extent, and rate of development of the pathological process. Thus, the highest incidence of positive results occurred among patients with brain tumors. Among these, results were almost invariably positive in infiltrating gliomas, with multiple lesions, and in tumors which involved the diencephalon and midbrain either directly or through increased intracranial pressure. On the other hand, a very low incidence of positive results was found in meningiomas, acoustic neurinomas, and pituitary tumors confined to the sella turcica.

These results have indicated that, besides its value as a diagnostic test, the amobarbital procedure might be useful prognostically and as an index of the degree of alteration in brain function. One method of investigating this problem is by serial testing of the same patient at different stages in the course of his illness and after

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* "Normal" is used to refer to persons in whom there is no demonstrable evidence of altered brain function.

therapeutic procedures. In this way it is possible to observe the relationship between changes in the amobarbital test results to changes in brain function as determined by other indicators, such as the clinical neurological signs, the EEG record, and other laboratory findings, for example, the cerebrospinal fluid protein content.

The purpose of the present study was to determine (1) whether any useful quantitative evaluation of the amobarbital test could be made which would adequately discriminate varying degrees of altered brain function; (2) whether changes in the test results are related to other indications of alteration in brain functions; (3) whether the test is of prognostic value, and (4) whether further validation of the differentiating value of the procedure could be established by using the patient as his own control.

METHOD

Immediately before and during the administration of the drug each patient was examined systematically for orientation and awareness of illness, using a standard series of questions, as follows: What is today's date? What month is it? What year is this? What time is it now? What part of the day? Where are you now? What is the full name of this place? What kind of a place is this? Where is this place located? How far from here do you live? Have you been out of the hospital at any time since you came here? Where were you last night? Have you been in any other hospital of this name? Who am I? Have you seen me before? Is there anything the matter with you? Are you sick? Why did you come here? What is your main trouble? Do you have . . . (mentioning specific symptoms or disabilities)?

The amobarbital sodium was given intravenously, in a solution of 0.5 gm. in 10 cc. of distilled water at a rate of 0.05 gm. per minute. As the drug was administered, the patient was asked to count backward from 100 to 1. The injection continued until the patient showed rapid nystagmus on lateral gaze in both directions, slurred speech, errors in counting backward, and drowsiness. These were regarded as physiological indicators of the effect of the drug. The total amount of amobarbital given to a patient depended on the appearance of a maximal physiological effect. The quantity actually given ranged from 0.1 to 0.5 gm., and in a few instances, 0.7 gm.

As soon as the physiological effects of the amobarbital sodium were manifested, the patient was again interviewed with the identical questions used in the preinjection examination. When a patient made an error, the question was asked immediately, as well as several times later, to determine the persistence of the error. In any case, all the questions were repeated at least twice during the interview with the drug.

In the previous study,[3] 11 patterns of denial of illness and disorientation were found to occur persistently only with patients with brain disease. These patterns were the patient's (1) stating that he was in some place unrelated to a hospital, such as home or a night club; (2) misnaming the hospital, either calling it by the name of another hospital or giving an apparently fictitious name; (3) describing the place as some variant of a hospital, such as "sanitarium"; (4) displacing the location of the hospital to another part of the city or to another city, or making gross errors in the distance from his home; (5) confabulating that he had been in another hospital with the same name as this one and with similar personnel and physical attributes (reduplication); (6) confabulating a journey, such as going home during the period of his hospitalization; (7) inversion of day and night; (8) misidentification of the examiner or the patient's statement that he had known the examiner before coming to the hospital; (9) complete denial of any illness; (10) denial of major aspects of illness, such as hemiplegia, but awareness of minor aspects, such as poor appetite, and (11) confabulating the nature of his illness. The persisting manifestation on repeated questioning of at least one of these patterns of behavior was regarded as a "positive" reaction.

METHOD OF QUANTIFICATION

Among the patients who showed positive results there was marked variation in the number of significant behavioral changes shown. One patient might be disoriented only for place, while another showed several of the patterns of disorientation and denial of illness. On the basis of a + to + + + + system of scoring, the results could be classified as follows:

+	Only one pattern of significant behavioral change
++	Two or three patterns
+++	Four or five patterns
++++	Six or more patterns

MATERIAL

A total of 34 patients have been tested with the amobarbital procedure on at least two or more occasions. These can be divided into five groups.

(*a*) Nine patients in whom clinical improvement was noted. In seven this occurred spontaneously; in two improvement accompanied roentgen therapy.

Cerebrovascular disease	4
Meningoencephalitis	1
Head injury	2
Third ventricle tumor	1
Postcraniotomy for pituitary tumor	1

(*b*) Two patients in whom the clinical signs became worse

Metastatic involvement of the central nervous system	2

(*c*) Eleven patients in whom the clinical picture remained essentially unchanged

Cerebrovascular disease	1
Postencephalitic Parkinsonism	2
Degenerative disease of the central nervous system	4
Olfactory groove meningioma	1
Metastatic involvement of the central nervous system	2
Prefrontal lobotomy	1

(*d*) Six patients who were tested before, during, and after E.S.T. for intractable pain

Spinal cord tumor	1
Dystonia musculorum deformans	2
Atypical facial neuralgia	1
Diabetic neuropathy	1
Headache of unknown origin	1

(*e*) Six patients were tested before and after operation for an intracranial neoplasm

Right parietotemporal meningioma	2
Frontal lobe meningioma	2
Cerebellar astrocytoma	1
Pinealoma	1

RESULTS

Patients with Clinical Improvement.—In Table 1 the data are shown for all the patients who showed clinical improvement. It can be seen that in all but two cases the result of the amobarbital test changed from a positive to a negative one. In most instances the behavior under the drug improved despite the fact that larger doses of the drug were given on subsequent testing.

The following cases are illustrative of this group of patients.

CASE 2.—*Improvement in cerebrovascular disease.*

A 60-year-old man was admitted to the Mount Sinai Hospital on Jan. 23, 1950. On Nov. 15, 1949, he had developed a transitory paralysis of the left lower extremity, followed three days

later by weakness of the left upper extremity, which persisted. On Jan. 3, 1950, he again developed paralysis of the left lower limb. Neurological examination showed severe weakness of the left limbs with increased deep reflexes and a Babinski sign. Sensory status showed occasional extinction of tactile stimuli in the left lower extremity on double simultaneous stimulation. The patient was facetious and euphoric and joked about his disability. At other times he expressed paranoid feelings. The EEG on Jan. 25 showed irregular delta activity, with frequencies as low as 1.5 per second at the right frontal, inferior frontal, and ear-lobe electrodes.

There were symmetrical bursts of high-voltage activity in the frontal area bilaterally. An amobarbital test was carried out on Jan. 26. After 0.35 gm. the patient stated that he had gone to "McCreery's Hotel" and later to "a furniture store," then to "Altman's" and "Gimbel's." Despite repeated questioning, he persisted in these confabulations. The patient denied that there was anything wrong with his left limbs and claimed that he could walk well. He stated that he was in the "Henry Hotel in Pittsburgh" and later in the "Mount Sinai Annex."

The patient's clinical course was one of improvement. An EEG taken on Feb. 10 showed a slighter degree of delta activity on the right side and infrequent bursts appearing only at the

TABLE 1.—*Change in Amobarbital Test Results Accompanying Clinical Improvement*

Case No.	Diagnosis	Dose for Each Test, Gm.		Time Interval After First Test, Wk.	Test Results
1	Head injury	(1)	0.4	..	++
		(2)	0.35	5	−
2	Cerebrovascular disease	(1)	0.35	..	+++
		(2)	0.45	3	−
3	Posteraniotomy for pitultary tumor (roentgen therapy)	(1)	0.3	..	+++
		(2)	0.4	2½	++
		(3)	0.3	11	+
		(4)	0.5	56	−
4	Cerebrovascular thrombosis	(1)	0.1	..	+++
		(2)	0.45	2	+
5	Meningoencephalitis	(1)	0.3	..	+++
		(2)	0.25	3	++
		(3)	0.3	6	−
6	Subarachnoid hemorrhage	(1)	0.3	..	++
		(2)	0.5	2	−
7	Cerebrovascular disease	(1)	0.5	..	++
		(2)	0.5	2	−
8	Head injury	(1)	0.4	..	++
		(2)	0.5	3	−
9	Third ventricle tumor (roentgen therapy)	(1)	0.2	..	++++
		(2)	0.45	65	++

right inferior frontal electrodes. Power increased in both left extremities and by Feb. 14 he was able to walk with assistance. When 0.45 gm. of amobarbital sodium was given on Feb. 16, the patient showed neither disorientation nor denial of illness. After discharge his power continued to improve, and examinations on Feb. 8 and May 10, 1951, showed only mild residuals of the left hemiparesis.

Comment.—In this patient the improvement in the clinical status and in the EEG record was paralleled by the results of amobarbital tests. While the first test showed marked disorientation and delusions of denial of illness, the second was normal. This change was useful in prognosticating eventual recovery.

CASE 3.—*Improvement following craniotomy and roentgen therapy.*

A 33-year-old German-born salesman was admitted to the Mount Sinai Hospital on Jan. 31, 1949. For the past six months he had had episodes of blurring vision and for a year had been sexually impotent. A right homonymous inferior quadrant defect of the visual field was noted on examination, and on Feb. 18 a craniotomy and biopsy disclosed a chromophobe adenoma of the pituitary gland.

After operation the patient developed a subarachnoid hemorrhage, was disoriented for time and place, and denied having had an operation. The details of this disorientation have been described in a previous paper.[2]

The disorientation persisted until March 22. At that time the patient's behavior appeared normal. On April 5 an amobarbital test was carried out. After 0.4 gm. he stated that he was in a hospital in Neuheim, Germany. He denied having had an operation and said a bandage had been put on his head because it was dirty. He denied receiving roentgen therapy, which he was getting at the time. He confabulated that he had gone to a "theater" the previous night. He then stated that he was in a "summer hotel" which was called Mount Sinai Hospital. He then said that he was in New York, which was a part of Canada.

A second amobarbital test was conducted on April 23. After 0.4 gm. he stated he was in "Hotel Neuhaus" and also in Mount Sinai Hospital. When the question was repeated, he said he was in Mount Sinai Hospital. He admitted having an operation but said it had been on his back. He admitted also that he was receiving roentgen therapy. Later in the interview he stated that he was in Mainz, Germany, on business and said he was in a restaurant.

A third amobarbital test, on June 22, showed a confabulated journey as the only manifestation of disorientation. He admitted having had an operation and gave its character accurately and named and located the hospital correctly. He said he had visited a friend the previous evening.

A fourth amobarbital test was given on May 2, 1950. After 0.5 gm. of amobarbital sodium he remained completely oriented and showed no denial of illness.

After discharge from the hospital, the patient continued to be sexually impotent. He would speak of this in a joking, unconcerned way. At the time of his last admission, however, he expressed considerable anxiety over his condition, for the first time.

TABLE 2.—*Change in Amobarbital Test Results Accompanying Clinical Deterioration*

Case No.	Diagnosis	Dose for Each Test, Gm.	Time Interval After First Test, Wk.	Test Results
10	Metastatic disease of the central nervous system	(1) 0.35	..	++
		(2) 0.35	1	++++
11	Metastatic disease of the central nervous system	(1) 0.4	..	−
		(2) 0.4	2	++++

Comment.—The successive amobarbital tests indicate the gradual improvement in brain function following the craniotomy. Although routine clinical procedure showed no evidence of disturbance of brain function one month after operation, two amobarbital tests indicated the presence of dysfunction. The third amobarbital test, which was slightly positive, indicated improvement, while one year after the craniotomy no evidence of altered brain function could be demonstrated under the influence of the drug. It is of significance that as long as impairment of brain function could be demonstrated by this method, the patient showed no anxiety about his sexual impotence.

Patients with Clinical Deterioration.—In Table 2 the data are shown for the two patients whose clinical picture became worse. Although the dose was the same for each test in the two patients, it can be seen that the second test showed markedly increased disturbance in behavior. Only two patients are listed, because in others the progressive course of the disease resulted in the appearance of disorientation which could be noted even without drugs.

The following case is presented in detail to illustrate the relationship between the change in the amobarbital test result and the clinical condition.

CASE 10.—*Deterioration with metastatic brain involvement.*

A 62-year-old man was admitted to the Mount Sinai Hospital on March 13, 1951, complaining of pain and stiffness in his neck over a period of four weeks.

Neurological examination showed no abnormality, but x-ray examination of the chest showed a large mass in the right lung, interpreted as a neoplasm. Cerebrospinal fluid protein was 104 mg.

per 100 cc. The EEG record was normal. Because of the suspicion of an intracranial metastasis, an amobarbital sodium interview was carried out on March 20. Prior to administration of the drug the patient was completely oriented and admitted his symptoms of headache and nuchal pain. After the injection of 0.25 gm., nystagmus and slurred speech appeared. After 0.3 gm. he stated he was in "Montefiore Hospital" but corrected this immediately. When the question was repeated several minutes later he referred to the hospital as "Monticello." The date was given as March 21, 1941. At the end of the interview he again called the hospital Mount Sinai.

In the week following the first amobarbital test the patient became more lethargic and retarded. Slight ataxia developed in the left upper extremity, and bilateral papilledema was noted. A second amobarbital test was done on March 26. After 0.25 gm. the patient stated he was in "Mount Zion" Hospital. After 0.3 gm. he said he was in "Monta Zinai" Hospital and located it on 131st St. He gave the date as March, 1940, and 1949. After 0.35 gm. the time was given as 7:20 in the evening (actually, 2:00 p. m.); he confabulated that he had gone home for breakfast and located himself at 48th St. and 86th Ave., in a union office. He stated that he had formerly been sick but was not ill at present and denied having been in a hospital recently.

TABLE 3.—*Amobarbital Test Results Accompanying Stability of Clinical Condition*

Case No.	Diagnosis	Dose for Each Test, Gm.	Time Interval After First Test, Wk.	Test Results
12	Olfactory groove meningioma	(1) 0.5	..	+
		(2) 0.35	12	++
13	Prefrontal lobotomy	(1) 0.75	..	+++
		(2) 0.75	3	+++
14	Degenerative disease	(1) 0.25	..	++
		(2) 0.4	½	+++
15	Postencephalitic Parkinsonism	(1) 0.45	..	++
		(2) 0.5	55	+++
16	Cerebrovascular disease	(1) 0.125	..	++++
		(2) 0.2	2	+++
17	Degenerative disease	(1) 0.3	..	++
		(2) 0.35	2½	+
18	Metastatic disease of central nervous system	(1) 0.4	..	++
		(2) 0.3	2	++
19	Degenerative disease	(1) 0.4	..	+++
		(2) 0.4	1½	++
20	Metastatic disease of central nervous system	(1) 0.3	..	++
		(2) 0.35	1	+
21	Degenerative disease	(1) 0.4	..	++
		(2) 0.4	6	++
		(3) 0.35	8	++
22	Postencephalitic Parkinsonism	(1) 0.5	..	++
		(2) 0.3	3	++

A ventriculogram performed on March 28 showed symmetrical dilatation of both lateral ventricles and rotation of the third ventricle. A suboccipital craniotomy was performed on the same day and revealed no tumor. On April 2 the patient was noted clinically to be euphoric and was disoriented for place, calling the hospital "Monta Sania," apparently a condensation of Montefiore and Morrisania. He continued to show disorientation and increasing incapacity until his discharge from the hospital, on May 29.

Comment.—The first amobarbital test provided evidence of intracranial involvement when the clinical examination and EEG record were normal. The worsening in the patient's condition and the appearance of definite neurological signs were paralleled by a more severely abnormal amobarbital test. The behavior during the tests prognosticated the type of disturbed behavior shown after the operation with the further progression of the disease.

Patients with Stability of Clinical Condition.—The data for the group of patients whose clinical condition remained essentially unchanged are shown in Table 3. The results of the amobarbital test varied on the different occasions tested, but they were always positive and never varied by more than 1 + in the scoring.

Patients Receiving Electroshock Therapy for Intractable Pain.—The data on serial amobarbital tests in patients receiving E.S.T. for intractable pain is shown in Table 4. Prior to E.S.T. the amobarbital test for each patient gave negative results. When retested after receiving E.S.T., four of the six patients had a positive reaction. Three of the patients who were positive during this period were retested later after cessation of the treatment and once more showed negative results. It is of interest that the two patients who were negative while receiving E.S.T. showed the least change of all in their clinical behavior accompanying the treatment and gave no indication of getting even transitory relief from their pain.

The following case is illustrative of the change in results of the amobarbital test accompanying E.S.T.

Case 24.—A 46-year-old woman entered the Mount Sinai Hospital on Jan. 8, 1952, because of pain in the right shoulder and right lower extremity of two years' duration. The patient

Table 4.—*Change in Amobarbital Test Results Accompanying E.S.T. for Intractable Pain*

Case No.	Dose for Each Test, Gm.	Relation to E.S.T.	Test Results
23	(1) 0.2	Before E.S.T.	—
	(2) 0.35	3 days after 19th E.S.T	+
	(3) 0.3	14 days after last E.S.T.	—
24	(1) 0.25	Before E.S.T.	—
	(2) 0.35	Before E.S.T.	—
	(3) 0.25	1 day after 7th E.S.T	+++
	(4) 0.15	4 days after 15th E.S.T.	++
	(5) 0.15	10 days after E.S.T. #18	—
25	(1) 0.5	Before E.S.T.	—
	(2) 0.5	1 day after 10th E.S.T.	+++
26	(1) 0.35	Before E.S.T.	—
	(2) 0.4	1 day after 10th E.S.T.	++
	(3) 0.5	After completion of E.S.T.	—
27	(1) 0.5	Before E.S.T.	—
	(2) 0.5	1 day after 10th E.S.T.	—
28	(1) 0.5	Before E.S.T.	—
	(2) 0.5	5 days after 13th E.S.T.	—

had been diabetic for at least 26 years. Because analgesics, dorsal sympathectomy, and stellate ganglion blocks had all failed to relieve her pain, a course of E. S. T. was initiated.

The amobarbital tests were held prior to the administration of the shock treatment. Both were negative, the patient remaining oriented and expressing awareness of her pain and diabetes. Clinical improvement was noted after the sixth treatment in that the patient did not complain spontaneously of pain. A third amobarbital procedure on Feb. 7, one day after her seventh shock treatment, was positive. She became disoriented for place, saying she was home; at another time she confabulated a trip home and persistently denied ever having had any pain in her shoulder and leg. She also misidentified the examiners. Another amobarbital test, four days after the 15th E.S.T., yielded disorientation for place (home), a confabulated journey, and the statement that the only thing wrong with her was that she was "tired." The denial of pain was not sustained as long as in the previous test. A fifth amobarbital procedure, performed 10 days after E.S.T. 18, was negative.

The EEG record on admission was normal. A small amount of moderate-voltage (50 mv.) sporadic 5 to 6 cps activity was noted bitemporally. A second EEG record, taken on Feb. 7, after the seventh E.S.T., showed considerably more delta activity.

Patients Tested Before and After Operation for Intracranial Neoplasm.—The data on patients with intracranial neoplasm tested before and after operation are shown in Table 5. In only one case (30) did a positive result become negative. In two cases (30 and 33) total removals were carried out. In the others partial removals were done, and one patient (Case 32) also received roentgen therapy.

The following case of recovery following total removal is presented in detail.

CASE 30.—A 51-year-old woman was admitted to the Mount Sinai Hospital on Aug. 16, 1952. Six months previously she had had the first of four convulsive seizures. Neurological examination showed a slight left facial weakness, slight weakness of the left lower extremities, and increased deep reflexes on the left side. Lumbar puncture yielded a clear fluid under normal pressure containing a total protein of 118 mg. per 100 cc. The EEG record showed focal slowing in the right temporoparieto-occipital region. On March 21 the patient was given 0.375 gm. of amobarbital sodium and became disoriented for place, saying she was in the examiner's apartment, and confabulated that she had gone out the night before.

On Aug. 29 a craniotomy was performed and a completely encapsulated tumor, approximately 4 by 3 cm. was removed *in toto* from the right parietotemporal region. Histological examination showed a meningioma of a fibrous meningothelial and angioblastic type.

Neurological examination on Sept. 9 showed persistence of the slight left facial weakness and slight paresis of the left upper extremity. Two-point discrimination was impaired in the fingers of the left hand. On Sept. 10 the administration of 0.35 gm. of amobarbital sodium produced no significant change in behavior. As of March 17, 1953, she has had no seizures,

TABLE 5.—*Amobarbital Test Results Before and After Craniotomy*

Case No.	Diagnosis	Dose for Each Test, Gm.		Time Interval After First Test, Wk.	Test Results
29	Cerebellar astrocytoma	(1)	0.3	..	++++
		(2)	0.5	28	+++
30	Parietotemporal meningioma	(1)	0.375	..	++
		(2)	0.35	3	—
31	Parietotemporal meningioma	(1)	0.5	..	++
		(2)	0.4	3	++
32	Pinealoma	(1)	0.15	..	++
		(2)	0.15	76	++
33	Olfactory groove meningioma	(1)	0.35	..	++
		(2)	0.35	4	+
34	Olfactory groove meningioma	(1)	0.5	..	++
		(2)	0.5	4½	+++

and examination showed only the slight facial weakness and diminished arm swing on the left. The sensory changes had cleared completely.

Comment.—The changes in the result of the amobarbital test paralleled the improvement in the symptoms and neurological signs following the total removal of the tumor.

GENERAL COMMENT

In the previous study on the use of amobarbital sodium as a diagnostic test,[3] the effects of the drug on a group of patients with brain disease were compared with those on a normal control group without involvement of the central nervous system. In the present investigation, patients with alterations of brain function were tested at successive stages in the course of their illness, each patient thus serving as his own control. In those cases in which the clinical course did not change, the results of the amobarbital test were consistently positive within a variation of 1 +. In those patients in whom there was definite improvement or deterioration, the amobarbital tests showed a parallel change. These findings establish further the validity of the procedure as an index of alteration in brain function.

The procedure should be useful in patients in whom brain disease is manifested by subjective symptoms and behavioral changes rather than motor and sensory defects. In the latter, improvement in the use of a limb may be equated with improvement of brain function. However, in certain cases, while the pathological process is

clearing, a patient may become depressed and agitated and even show psychotic manifestations.† Conversely, as brain damage progresses, a hitherto anxious or depressed person may develop a calm equanimity or euphoria and deny all symptoms.[1] In Case 3, the patient showed a casually indifferent attitude toward his continued sexual impotence during the periods when his amobarbital tests were positive. His behavior might have been considered only as a neurotic mechanism of evasion and compensation were it not for this evidence of altered brain function. At a time when the amobarbital test was finally negative, indicating no demonstrable alteration in brain function, the patient showed great concern and anxiety over his impotence.

The data on patients receiving E. S. T. show that the test may serve as a sensitive indicator of changes in brain function which are not detectable by ordinary clinical methods or psychometric testing. No changes in behavior, mood, or the attitudes relating to pain during the course of treatment were shown by the two patients who had consistently negative amobarbital tests despite the same number and frequency of convulsions as the others. The four patients who showed mood changes and denied having pain, on the other hand, showed positive results with the amobarbital procedure. The method thus may provide a tool for the further investigation of the nature of the therapeutic action of electric shock.

The behavior that has been described is a type of adaptation expressed in the verbal symbols of denial and disorientation. While an altered milieu of brain function is necessary for the persistence of these manifestations, some persons under similar conditions of function use other symbolic forms. Thus patients receiving the drug may become very drowsy, restless and unresponsive and answer few questions, so that their quantitative scores are low. We have suggested elsewhere ‡ that such drowsiness and withdrawal not only are direct physiological effects of the drug, like nystagmus, but have symbolic aspects related to individual personality differences. While high scores tend to be associated with the severer and more prolonged impairments of function, it cannot be stated then that a higher quantitative score means a greater degree of brain damage in comparing one patient with another. However, when the mode of adaptation is already known in an individual patient, then a change in the results of the test procedure is significant.

SUMMARY AND CONCLUSIONS

Thirty-four patients were given the amobarbital test ("amytal test") for brain disease serially at different stages of their illness.

A method of quantifying the test data is proposed. It was found that the results of the test paralleled improvement or deterioration of brain function as indicated by other methods of study.

The serial use of the amobarbital procedure should be of particular value in the study of patients with brain disease, with changes in behavior and in conditions in which the alterations of brain function are poorly understood, as after electric shock treatment.

It is concluded that the test is a valid method of indicating a present degree of alteration of brain function, change from a previous level of functioning, and of prognosticating the subsequent course.

† References 4 and 5.

‡ References 5 and 6.

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CHLORPROMAZINE

New Inhibiting Agent for Psychomotor Excitement and Manic States

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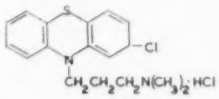
THROUGHOUT its history psychiatry has been faced with the therapeutic problem of controlling acute and chronic states of psychomotor excitement. Much has been achieved with the advent of systematic pharmacological sedation. More recently the introduction of electroconvulsive treatment has augmented our capacity to handle successfully most of the excited states refractory to sedation by drugs. There remain, however, a number of cases in which one meets particular difficulty in controlling excitement either because of undesirable side-effects of the treatment itself or because of the patient's persistent tendency to relapse. It is the purpose of this article to report on our experiences with a new drug which seems to possess specific properties for the psychiatric management of excited states.

The first clinical investigations with this drug were carried out and published in France,* where it is known as Largactil,† or 4560 R. P. It is known by the same name in Canada. In the United States it is referred to as chlorpromazine, or Compound 2601-A. Chlorpromazine has been developed in the Rhône-Poulenc Special Research Laboratories during research on potentiating agents in anesthesia.

PHARMACOLOGY ‡

Chlorpromazine is a phenothiazine derivative with the following formula:



Its chemical designation is 3-chloro-10(3-dimethylaminopropyl)phenothiazine hydrochloride. The molecular weight is 335.320; the melting point, 179-180 C. It is highly soluble in water, chloroform, and ethyl and methyl alcohol. A 5% aqueous solution is stable for at least 24 hours and has a pH of 4.9. It is a gray-white crystalline powder, which is photosensitive and will change color when exposed to light.

From the Verdun Protestant Hospital.

* References 1 and 2. Delay, J., and Deniker, P.: Réactions biologiques observées au cours du traitement par le chlorhydrate de diméthylaminopropyl-N-chlorophénothiazine (4560 R.P.), Congrès des psychiatres de langue française, Luxembourg, July 22-26, 1952. Reference 3.

† Poulenc, Ltd., supplied us with a generous amount of Largactil, which has made it possible to undertake this study.

‡ Information published by Rhône-Poulenc Special Research Laboratories, and Smith, Kline & French Laboratories.

It is chemically related to promethazine (Phenergan) and diethazine hydrochloride (Diparcol), which are also phenothiazine derivatives and are used as antihistaminic agents and in the treatment of Parkinsonism.

In a group of dogs given 20 mg. per kilogram daily for a month the mortality was nil. Chlorpromazine produced a type of depression in animals which increased progressively with the dose. Hypnosis has never been observed.

The drug has a pronounced antiemetic action and in dogs decreases the vomiting frequency following administration of apomorphine hydrochloride, 40 to 100%.

The vasopressor activity of small doses of epinephrine in cats is reversed by chlorpromazine, which possesses a mild adrenergic blocking activity. It does not modify in any way the hyperglycemia produced by epinephrine. The drug inhibits the secretion of gastric juice and reduces the incidence of gastric ulcers in rats in which a ligature of the pylorus has been performed.

A hypothermic effect is observed in rats, in which the body temperature drops 1-6 C. after the administration of chlorpromazine.

The drug exhibits a moderate antihistaminic activity. A marked potentiating effect is observed when it is administered in combination with sedatives, general anesthetics, analgesics, and ethyl alcohol.

Blood levels and elimination of the drug were studied experimentally with rabbits and reported by the Poulenc laboratories. After oral administration of a dose of 250 mg. per kilogram, the blood concentration rose to its highest level of 8 mg. per liter in three hours. The total quantity excreted by the kidneys in three days represented only 7-8% of the intake, suggesting that the major proportion of the drug is metabolized in the organism before it reaches the kidneys.

PHYSIOLOGICAL EFFECTS IN HUMANS

The most striking effect of the administration of chlorpromazine in humans is a pronounced drop in blood pressure, which may vary from 20-40 mm. systolic and 10-30 mm. diastolic, according to dosage and individual response. While the blood pressure tends to remain below the normal level of the individual subject, one observes frequent fluctuations upward and downward. A compensatory tachycardia is usually observed as the pulse rate rises from 10-40 beats per minute. A distinct pallor is noted in most subjects, and many exhibit miosis.

The majority of our patients evidenced mild hyperthermia, with ranges from 99 to 101 F. for the first few days of treatment. In each case the fever subsided spontaneously, and in some instances was followed later by hypothermia, with the temperature ranging between 96 and 98 F.

The respiratory rate is not influenced by the drug. Dryness of the mucous membranes and nasal congestion are frequent findings, particularly at the commencement of therapy. Urinary frequency is commonly observed and is possibly due to increased renal blood flow. There is often a tendency to constipation. The appetite remains very good, and most patients gain weight during treatment.

Patients receiving large doses of chlorpromazine exhibit definite motor retardation, with an unsteady gait, while the facial expression becomes rather wooden and the general appearance resembles that of Parkinsonism but there is no muscular rigidity. With smaller doses these phenomena are less pronounced. There is usually marked drowsiness, which may increase to the point of somnolence. Deep and superficial reflexes may be unaltered or slightly depressed.

These symptoms are reflected in the patients' statement that they feel cold, drowsy, faint, and weak. The effects of the drug persist for about 48 hours after termination of treatment.

ADMINISTRATION AND DOSAGE

Delay, Deniker, and Harl [4] were the first clinicians to employ chlorpromazine as the sole drug in psychiatric conditions. Similarly, we have used the drug by itself rather than in combination with other antihistaminics or sedatives because of the obscuring effects of "potentiation" which chlorpromazine then produces. Deschamps [5] has administered the drug in conjunction with promethazine and barbiturates.

Patients differ considerably in their reaction to chlorpromazine. Administered parenterally, the drug is much more effective than when given orally. Tolerance develops rapidly and requires an increase in dosage after a few days to maintain a constant level of sedation. In our material we have found it necessary to employ doses which often considerably exceed those used by the French workers.

Depending on the patient's condition, we employ the drug in two ways, as a sedative for severely agitated patients and in states of moderate restlessness. In states of acute psychomotor excitement we have found it effective to begin giving 50 mg. intramuscularly twice a day, with use of 50 mg. orally two or three times a day. If the patient refuses oral medication, the parenteral dose may be increased. The aim is to produce a state of motor retardation, emotional indifference, and somnolence, and the dose must be increased accordingly as tolerance develops. After the first week of treatment the patients remain retarded but are less sleepy. In most cases it has not been necessary to exceed a dose of 800 mg. per day, while some patients may require only 100 mg. or less daily. The course of treatment may last from three days to four weeks. We have not observed withdrawal symptoms even when the drug is abruptly discontinued, although it is advisable to reduce it gradually. It should be noted that parenteral administration is more reliable in its effects than oral administration.

In less pronounced psychomotor restlessness or emotional tension, such as that seen in long-standing anxiety states, senile agitation, and certain behavior disorders, the administration of the drug may have to be continued for two or three months, and in these cases 25 to 50 mg. two to four times a day is given orally. With this amount the patients are not drowsy once tolerance has developed and are able to remain active and composed.

Intravenous administration of the drug requires dilution with isotonic saline because of its relatively low pH and the danger of damaging the venous endothelium. Intramuscular administration is safe but somewhat painful, and for this reason it is recommended to dilute the drug with distilled water, saline, or procaine. In none of our patients did abscesses develop at the site of injection.

Blood pressure, pulse rate, and temperature are charted at least twice daily. Results of urinalysis, including tests for bile, and body weight are recorded every week. A simple and sensitive liver function test should be done at the beginning of treatment. In our material the cephalin-cholesterol flocculation test has been used.

No special diet is required. The patient's appetite remains good as a rule, and laxatives may be necessary if constipation develops. Bed rest is recommended, at least during the first week, if larger doses are employed, because of the orthostatic

hypotension which develops in most cases during treatment and which may lead to syncope in ambulatory patients. It is important to note that ordinary analeptics seem to have little effect on the depression of the autonomic and central nervous systems produced by chlorpromazine. Caffeine, aminophylline, and phenylephrine (Neo-Synephrine) may be tried, although in most cases lowering the patient's head and elevating the legs will suffice. Pentylenetetrazol (Metrazol) and nikethamide (Anacardone; Coramine) are contraindicated if chlorpromazine has been given previously. One of our patients who had collapsed owing to orthostatic hypotension and the resulting cerebral anemia was given 2 cc. of nikethamide by error and developed a series of generalized convulsions, from which he recovered within an hour. Precautions should be taken against upper respiratory infections because of the dryness of the mucous membranes which often develops in the course of treatment.

The following is an outline of our ward procedure:

1. Give deep intramuscular injection; do not administer intravenously.
2. Dilute 1 cc. of the drug with 1 cc. of isotonic saline.
3. Rotate sites of injection (right and left deltoid, right and left buttock, and right and left lateral aspect of thigh).
4. Do not inject more than 2 cc. at one place.
5. Start patient on "bedside notes."
6. Encourage patient to remain in bed.
7. Make weekly urinalyses (check for bile) and body weight determinations.
8. Give no other medication while patient is on chlorpromazine, except on special order.
9. Chart blood pressure, pulse rate, respiration rate, and temperature every 12 hours.
10. Give regular diet.
11. Protect patient against cold.
12. Give enema if necessary.
13. In case of syncope or collapse, place patient in horizontal position with legs elevated. Do not give nikethamide or Metrazol.

PSYCHOLOGICAL EFFECTS

Chlorpromazine has a pronounced inhibitory effect on certain functions of the central nervous system. Patients receiving the drug become lethargic. Manic patients often will not object to bed rest, and patients who present management problems become tractable. Assaultive and interfering behavior ceases almost entirely. The patients under treatment display a lack of spontaneous interest in the environment, yet are easily accessible and respond as a rule immediately and relevantly to questions even if awakened from sleep. As Delay and Deniker § described them, they tend to remain silent and immobile when left alone and to reply to questions in a slow monotone. We can confirm the observations of these authors that patients receiving the drug are often aware of their improvement without showing any euphoric reaction.

Some patients dislike the treatment and complain of their drowsiness and weakness. Some state that they feel "washed out," as after an exhausting illness, a complaint which is indeed in keeping with their appearance. Others, however, appreciate the peculiar effect of the drug which allows them to relax from ideational pressure. One manic patient stated after her recovery that with the drug she soon

§ Delay, J., and Deniker, P.: Trente-huit cas de psychoses traitées par la cure prolongée et continue de 4560 R.P., Congrès des psychiatres de langue française, Luxembourg, July 22-26, 1952.

lost the feeling: "I had to live my whole life in one day." Another patient suffering from long-standing anxiety described thus the effect of small doses of chlorpromazine on her feelings: "It was like a chairman taking control of a meeting where everybody previously had been shouting at once."

Although a patient under the influence of chlorpromazine at first glance presents the aspect of a heavily drugged person, one is surprised at the absence of clouding of consciousness. The higher psychic functions are preserved to a remarkable degree, and the patients are capable of sustained attention, reflection, and concentration.

In a series of eight experimental subjects, tests of reaction time, hand steadiness, tapping speed, digit span, and digit symbols (Wechsler-Bellevue subtest) were given one and a half hours before and one and a half hours after the administration of a dose of chlorpromazine sufficiently large to promote definite somnolence. In three subjects the reaction time was significantly shortened; in two, prolonged; in three, unchanged. Hand steadiness was improved in two subjects, impaired in none, unchanged in six. Tapping speed showed the most pronounced impairment, being slowed down significantly in four subjects, accelerated in one, unchanged in three. Digit span was improved in five subjects, impaired in two, and unchanged in one. The digit symbol test was improved in six subjects, impaired in one, and unchanged in one. There was noted, then, definite improvement of functions involving attention and learning as tested in digit span and digit symbols, while coordination and speed of sensory-motor reaction also tended to improve under the test condition, rather than deteriorate. The only test reflecting impairment of function in 50% of our subjects was the tapping speed, which calls for an almost unstructured repetitive motor performance, the speed of which depends almost entirely on the subject's inner motivation, without extraneous stimulation or clue to the success of performance.

With three of these subjects the experiment was repeated a few days later after administration of 3 grains (0.195 gm.) of secobarbital (Seconal) sodium. They showed the typical effects of barbiturate sedation, namely, almost uniform impairment in all tested functions. Yet it was noted that two of these three patients appeared less sleepy after secobarbital than after chlorpromazine.

Thus, it becomes apparent that the sedative effect of chlorpromazine is not associated with clouding of consciousness, impairment of judgment, or disinhibition of affect. One has the impression that this drug promotes an attitude of sober resignation and of critical reflection, even in acutely disturbed patients. We can state that in our experience chlorpromazine is the only powerful sedative whose action is restricted to a selective inhibition of drive without producing disinhibition of affect at any level of dosage.

RESULTS

This report is based upon our experience in the use of chlorpromazine at the Verdun Protestant Hospital. Seventy-one psychiatric patients, ranging in age from 18 to 82 years, were treated over a period of four months.

The most gratifying results were obtained in the group of manic-depressive patients in the manic or hypomanic state. Psychomotor excitement is usually reduced significantly within 24 hours, and sleep at night is often restored within the same period. Only in the odd case may the addition of minimal doses of other sedatives

be required, the effect of which is greatly enhanced by chlorpromazine. Feeding problems disappear rapidly, and the patient soon becomes cooperative to nursing care. The psychiatrist is surprised to find his manic patients amenable to reason. The average duration of treatment for these patients varied from two to five weeks. Although some patients appear to be asymptomatic within a few days, it is advisable to continue the treatment for some time in order to avoid relapses. In keeping with good practice in managing the institutionalized manic patients, we have retained our patients in the hospital for at least two to three weeks after all symptoms have subsided and medication has been discontinued.

The drug is of unique value in the symptomatic control of almost any kind of severe excitement. This includes catatonic schizophrenia, schizoaffective conditions, epileptic clouded states, agitation occurring in lobotomized patients immediately or several months after surgery, and organic-toxic confusional states, as frequently observed in uremic conditions and senile psychoses. A single intramuscular dose of 50 to 100 mg. will usually control most states of excitement. If it is used in conjunction with other sedation, caution must be observed because of its potentiating effect.

In a few cases we had the impression that the immediate administration of the drug for three or four days prevented a psychotic breakdown in patients with a history of one or more psychotic episodes who were exhibiting their typical prodromal symptoms.

Emotional tension is well controlled by comparatively small doses of 50 to 200 mg. daily, amounts which have been administered without untoward effects to some psychoneurotic patients over a period of several months. A 82-year-old woman, whose agitated delirium had proved refractory to all other therapeutic methods, has been successfully controlled by the drug for a period of more than four months, without untoward effects. The possible toxic effect of chlorpromazine on the liver, however, requires caution when used for long periods of time, especially in patients with impaired liver function. The only death reported in the literature [5] occurred during the treatment of a patient with severe delirium tremens and cirrhosis of the liver.

Most of the patients who showed no lasting improvement with the drug were chronic schizophrenics presenting considerable deterioration. We have not observed a direct influence of the drug on delusional systems or hallucinatory phenomena. Delay and associates [6] reported one failure in the treatment of a cortisone-induced manic-confusional state, although they stressed the excellent effects of chlorpromazine in other acute attacks characterized by confusion.

Our therapeutic results are summarized in the accompanying Table.

We are particularly impressed with the favorable results in our manic-depressive patients in a chronic manic state, all of whom had been continuously manic or hypomanic for more than a year and had previously failed to respond to standard therapeutic procedures or had had only brief remissions. In some of these long-standing cases recovery with chlorpromazine may not be immediate, the improvement gradually progressing for a month or two after termination of therapy. In acute manic states chlorpromazine therapy usually leads to recovery in a shorter time than is required with other, established treatment procedures. It is generally known that the rapid remissions that follow electroshock therapy often are short-lived, while relapses following chlorpromazine therapy are not frequent.

In four patients, all manic-depressives in the manic phase and over 45 years of age, we observed an interesting inversion of clinical manifestations, as the patients under treatment with the drug became depressed after a brief remission, which lasted only a few days. The depressed state responded in the typical manner to electroconvulsive therapy, requiring only four to six electroshocks to effect a lasting recovery.

We have observed that psychiatric patients who fail to show the typical physiological changes of drop in blood pressure, rise in pulse rate, and slight fall in body temperature also often fail to give a satisfactory therapeutic response. It should be noted, however, that cardiovascular and thermal responses during the first few days of treatment can be very unstable, until a new equilibrium is established. Elderly patients, however, frequently fail to demonstrate the relative tachycardia at any time, although their therapeutic response may be satisfactory.

Chlorpromazine has sometimes given results when other treatments, including insulin and electric shock, have proved of no avail or have not produced complete

*Therapeutic Results with Chlorpromazine**

	Averted	Recovered	Much Improved	Improved	Unchanged	Still Under Treatment	Total
Schizophrenia	2	..	3	9	7	1	22
Schizoaffective	..	..	1	2	..	..	3
Manic, acute	2	8	2	7	..	3	22
Manic, chronic	..	4	1	3	1	3	12
Psychoneurotic	..	1	..	1	2	..	4
Postlobotomy	..	..	..	2	1	1	4
Mental deficiency	..	..	..	..	1	..	1
Senile psychosis	..	..	..	3	..	..	3
Total	4	13	7	27	12	8	71

* Averted means arrest of imminent psychotic attack during prodromal stage; recovered, sustained cessation of symptoms within 40 days; much improved, reduction of symptoms to the point where the patient is able to leave hospital within 40 days; improved, sustained lessening of symptoms within 40 days but patient unable to leave hospital.

remission. It is of particular value in patients who during a course of electroconvulsive therapy become violently excited. The fact that it does not produce emotional disinhibition gives chlorpromazine a special place in the treatment of acute hysterical agitation, where ordinary sedation might bring about further loss of control. Our material does not include cases of addiction, but one would expect it to be of value in managing withdrawal symptoms because of its dependable sedative action, most of which is free from euphoric effects.

On the other hand, the new drug should not be expected to be a cure-all in psychoneuroses. If moderate oral doses of 100 to 200 mg. per day do not give satisfactory relief from tension, higher doses will usually be of no avail. If traumatic factors cannot be excluded from the environment and major conflicts persist, chlorpromazine can only be considered an adjuvant to psychotherapy.

TOXICITY

It is our belief that chlorpromazine must be administered under close medical supervision, since the drug is capable of producing undesirable side-effects in a certain number of persons. As has been indicated, we consider the use of the drug

as a therapeutic procedure which preferably should be carried out in a hospital setting. Although safe outpatient treatment with this drug is possible, one must warn against unrestricted use of chlorpromazine as a sedative.

In our clinical material, about half the patients showed slight changes in the cephalin-cholesterol flocculation, a number of these being of questionable significance; 30% showed changes in total serum protein values and albumin-globulin ratios, most of them to a very minor degree. The sedimentation rate increased in about 50%, the changes remaining within normal limits in many cases. We observed no impairment of kidney function as measured by blood urea nitrogen values. Urinary findings remained normal throughout the period of administration. Hemoglobin and red and white cell counts were not altered significantly. Increased susceptibility to upper respiratory infection was noted and was probably related to the dryness of the mucous membranes. Delay and Deniker || assume a generally lowered resistance to infection, but we have not encountered any serious complications of this type in our material.

Nausea, anorexia, and epigastric distress have been observed by us in 8% of the patients. Allergic reactions, as manifested by urticaria or asthma, occurred in 13% of cases. These latter complications are interesting, inasmuch as the drug is reported to have powerful antiemetic properties and belongs in the class of antihistaminics. The allergic manifestations subside when the drug is discontinued. Gastrointestinal complications were not considered an indication to termination of the treatment.

In three patients treated for two, three, and four weeks respectively, jaundice developed, which appeared to be of toxic origin, with the attendant blood and urine abnormalities. These patients were symptom-free within 10 days after the drug was discontinued and a supportive dietary regimen instituted. Their cephalin-cholesterol flocculation tests were negative after two to three weeks.

Several patients were treated while ambulatory for four months with doses up to 200 mg. per day, without showing any untoward effects.

COMMENT

To justify its addition to the voluminous list of therapeutic agents in psychiatry, any new drug might be analyzed from the following aspects:

(*a*) Does it control symptoms as well as or better than other established treatments?

(*b*) Does it compare favorably with regard to ease of administration and unpleasant side-effects?

(*c*) Is there less risk associated with its use?

(*d*) Does it improve the underlying pathological condition?

(*e*) Does it permit sustained psychotherapeutic rapport?

It will be noted that the first four questions may be applied to any therapeutic agent in any branch of medicine, while the last one is of singular significance to

|| Delay, J., and Deniker, P.: Le traitement des psychoses par une methode neurolytique dérivée de l'hibernotherapie, Congrès des psychiatres de langue française, Luxembourg, July 22-26, 1952.

psychiatry. Many of us have in recent years lost sight of our essential task of understanding our patients, as we subject them to a sequence of comas, shocks, convulsions, confusion, and amnesia, all of which render them incapable of relating to the psychiatrist in a consistent and meaningful manner.

In the light of the questions formulated, we may consider the two principal psychiatric procedures currently employed in the treatment of the manic state of manic-depressive psychosis, namely, E.C.T. and standard pharmacological sedation, including prolonged sleep therapy, as compared with chlorpromazine treatment.

E.C.T. provides excellent and immediate control of symptoms if administered intensively. It may, however, by its disorganizing effect on the higher brain functions, produce a new set of symptoms, characterized by confusion, restlessness, and aggression.[7] While E.C.T. is one of the simplest forms of treatment, it is associated with the unpleasant side-effect of amnesia. The possible injuries to the musculoskeletal system and the complication that may arise from the use of relaxing drugs also constitute important disadvantages. In addition to its symptomatic effect on psychomotor excitement, E.C.T. terminates many manic attacks, but immediate relapses are frequent. Rapport with the therapist is possible only on the most superficial level, in many cases not all because of the confusion so often associated with the use of E.C.T.

In prescribing barbiturates, scopolamine, insulin, etc., as symptomatic sedation, failures are not uncommonly encountered because of the disinhibiting action of these drugs. However, their administration is extremely simple, and the patient, as a rule, does not experience unpleasant side-effects. While symptomatic control with these sedatives is associated with few risks, the dangers entailed in prolonged sleep therapy are serious and manifold in nature. To protect the patient against pneumonia, hyperpyrexia, and cardiovascular collapse, elaborate nursing procedures are necessary.[8] The clouding of consciousness resulting from the use of standard sedation hampers the therapist in maintaining rapport, even though repressed material may be released from the unconscious. Nevertheless, it has been claimed that prolonged narcosis is followed by fewer relapses than E.C.T. and is the most efficacious form of therapy in manic states, although its wider application is limited by its inherent dangers and difficult administration.

Chlorpromazine, in our experience, has been the most reliable psychiatric agent in the control of symptoms of psychomotor excitement. Its administration is more cumbersome than E.C.T. or ordinary sedation but much simpler than the complicated procedure required for prolonged sleep. Unpleasant side-effects with chlorpromazine are of minor significance. The use of the drug, particularly for extended periods of time in high doses, may be fraught with some risks, but under adequate medical supervision few difficulties should be encountered.

Chlorpromazine, by operating on the underlying pathological process, is capable of shortening the course of a manic attack. Perhaps the greatest advantage of this drug lies in its power to quiet severely excited patients without rendering them confused or otherwise inaccessible.

The mode of action of chlorpromazine has not yet been established. Several theories have been advanced. It has been surmised that the drug operates through an effect on general metabolism by lowering the cellular O_2 requirements. We

have not been able to confirm the findings of Delay and Deniker ¶ that basal metabolism is lowered after chlorpromazine administration. Nor could we corroborate their findings of a significant drop in the eosinophile count with chlorpromazine. We therefore do not feel justified at this time in assuming that the drug exhibits its specific effects through the adrenals or any other endocrine glands.

In contrast to barbiturates, chlorpromazine does not appear to alter the basic character of the individual E.E.G. as long as the subject is awake. It tends to produce clear tracings comparatively free from muscle artifacts and tension discharges. This finding is not surprising in view of the fact that the drug seems to have little effect on those psychological functions which have their representation in the cortex, but appears to affect selectively those subcortical structures that are concerned with maintaining psychomotor drive and wakefulness.

One may speculate from the above that cortical metabolism is little affected by chlorpromazine and that the possible site of its action is located in the activating reticular substance, the functions of which have recently been reviewed by Magoun.[9] Because of its ganglioplegic effects, one also would think of the hypothalamus as a locus of its action.

In reflecting on the possible chemical mechanism involved, one notes the close relation of the chlorpromazine formula to that of promethazine. The latter drug has been shown by Himwich [10] to possess antiacetylcholine properties in the neuraxis.

SUMMARY

Chlorpromazine is a new phenothiazine derivative related to certain antihistaminic agents. It has pronounced effects on the central nervous system. In animals, it produces a type of depression which increases progressively with the dose, has strong antiemetic properties, inhibits the secretion of gastric juice, and produces hypothermia.

In man it potentiates the effects of cerebral depressants, lowers the blood pressure, and accelerates heart action. It produces motor retardation, somnolence, and weakness. Allergic reactions occur infrequently. Reversible impairment of liver function may be observed if the drug is used in large doses over extended periods of time.

The lethargy resulting from the drug in contrast to other sedatives is characterized by clarity of consciousness and retained responsiveness, which has been demonstrated by experimental psychological methods. Chlorpromazine, at any dosage, does not produce emotional disinhibition but selectively inhibits drive, which makes it unique among the more powerful sedatives.

In this study chlorpromazine was not used in combination with other sedatives. Doses vary considerably with the individual subject and range from 50 to 800 mg. per day. Prolonged administration requires nursing and medical supervision.

Seventy-one psychiatric patients, ranging in age from 18 to 82 years, were treated over a four-month period. The drug has proved to be of unique value in the symptomatic control of most types of severe psychomotor excitement. Impressive

¶ Delay, J., and Deniker, P.: Réactions biologiques au cours du traitment par le chlorhydrate de diméthylaminopropyl-N-chlorophénothiazine (4560 R.P.), Congrès des psychiatres de langue française, Luxembourg, July 22-26, 1952.

therapeutic results were obtained in acute and chronic manic-depressive patients in the manic phase. Attacks are significantly shortened. Relapses are less frequent than with E.C.T.

Selective inhibition therapy with chlorpromazine is compared with two other standard treatments for manic conditions, i. e., E.C.T. and prolonged sleep. Little is known of the exact mode of action of the drug. A possible mechanism involving acetylcholine metabolism has been considered, and, on the basis of clinical evidence available, the reticular activating system in the brain stem is proposed as the site of action.

Dr. G. E. Reed, medical superintendent of the Verdun Protestant Hospital, permitted the publication of this report.

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NEUROLOGICAL AND ELECTROENCEPHALOGRAPHIC EFFECTS OF X-IRRADIATION OF THE HEAD IN MONKEYS

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LOS ANGELES

THE ADULT nervous system is highly resistant to ionizing radiation at dosage levels which severely injure other tissues.* In support of this generalization Eldred and Trowbridge have recently found that x-irradiation of monkeys with total-body doses of 400 to 800 r failed to induce neurological changes,[3] although radiation sickness and death occurred.[4]

It has been shown, however, that higher doses of radiation, when restricted to the heads of monkeys, may result in weakness, apathy, hemiparesis, and hemiplegia.[5] Similarly, tremors, clonic twitching, and epileptoid seizures have been seen after irradiation of the brains of puppies.† Lyman, Kupalov, and Scholz [8] and Nemenov ‡ believed that irradiation of the head in dogs caused impairment of reflex conditioning (Pavlov), while Warren [10] reported a "depression" of the nervous system in rats after 1,500 r total-body exposure. These investigations, together with case reports in man,§ indicate that the central nervous system can be damaged by high doses of ionizing radiation.

The use of electroencephalography as an index of subclinical cerebral injury following irradiation seems first to have been employed by Eldred and Trowbridge,[3] who noted no EEG abnormalities except in the premoribund stages of radiation sickness. In the present study generalized radiation sickness has been avoided by shielding all parts of the monkey below the neck, thus permitting the study of effects on the nervous system of considerably higher doses of x-rays than is practicable with total-body exposure. The numerous neurological and electroencephalographic abnormalities which followed doses of 1,500 to 6,000 r to the heads of monkeys are reported in the present paper. A few observations of other effects which may be of use in

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* References 1 and 2.

† References 6 and 7.

‡ References 7 and 9.

§ References 11 through 16.

interpreting the neurological findings are also presented. Neuronal and neuroglial pathology and changes in the blood-brain barrier are reported in an accompanying paper.[17]

METHOD

Thirty-seven monkeys (*Macaca mulatta*), ranging in weight from 1.7 to 3.7 kg., were used. The radiation was delivered by a 250 kvp G.E. Maximar machine, using 0.5 mm. Cu and 1.0 mm. Al filters. The HVL was calculated to be 1.4 mm. of Cu at a FOD of 35 cm., and the dosage rate was 118 r per minute, as measured by a Victoreen thimble chamber in the center of a Masonite phantom with a radial thickness of 4 cm. The head of each animal was exposed to the beam while the rest of the body was protected by 1/8 in. (32 mm.) lead shielding, through which less than 0.5% of the radiation penetrated (Fig. 1). Exposure was equalized by rotating the

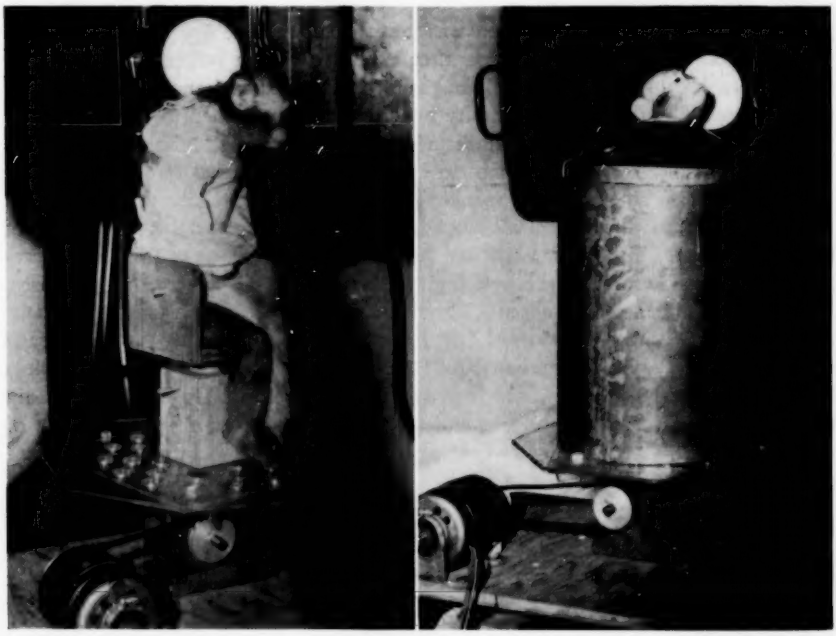

Fig. 1.—The method of irradiation is shown. At the left, the monkey is restrained in a chair on the rotating platform. At the right, the lead shield has been placed around the animal and its head is aligned with the portal of the x-ray machine.

animal at a rate of 1 rpm. Single doses were given at five levels: 6,000, 4,500, 3,000, 2,000, and 1,500 r (Table for details).

Physical examinations, EEG recordings, and observations of rectal temperature were made three times on each animal before irradiation and as frequently thereafter as the findings dictated. At similar intervals red and white blood cell, differential, and platelet counts were made on peripheral blood from 18 monkeys. During physical examinations emphasis was placed on observations concerning behavior, strength, reflexes, coordination, and sensory perception. Autopsies were performed on all animals. Some animals at each dosage level were allowed to succumb to the effects of irradiation or were killed when in a moribund state, in order to establish the survival time. Others were killed at intervals of from a day to six months following exposure (Table).

The EEG was recorded using steel phonograph needles as pick-up electrodes. Six bipolar leads—right and left frontoparietal, right and left parieto-occipital, transparietal, and transoc-

cipital—were connected to a six channel Grass Model III amplifier and ink writer. Waking tracings were taken on all animals; in addition, the stages leading to sleep induced by pentobarbital (Nembutal) sodium (35 mg. per kilogram, intramuscularly) were recorded in 12 of the animals.

RESULTS

Because the data obtained from the animals receiving 6,000 r and 4,500 r are very similar, these animals are considered together in a first group. Animals exposed to 3,000 r form a second group, and a third is composed of animals receiving 2,000 r and 1,500 r. All time notations refer to intervals following irradiation.

6,000 AND 4,500 R

General Observations.—During the process of irradiation the monkeys exhibited normal curiosity and showed no excessive excitation. Upon close inspection, no erythema, lacrimation, or salivation was noted, although the lips and cheeks were slightly swollen for about two hours after exposure. Upon return to the cage the animals drank copiously and ate, although in two to four hours they began to refuse food. Meanwhile, spontaneous activity progressively diminished to the extent that the monkey sat motionless when undisturbed. Later, at 6 to 12 hours, there was no resistance to capture and no attempt to escape when the animal was placed on the floor. It was also noted that the monkey's grip was weakened. As this apathy and asthenia increased, the animal's slumped posture gave way to the prostration of preterminal coma. By this time marked facial edema and profuse conjunctival secretion were present, together with petechial hemorrhages of the conjunctiva and irises. Vomiting and diarrhea were absent. Three animals exhibited Cheyne-Stokes breathing terminally. Within 55 hours, 12 of the 16 animals at these two highest dosage levels died or were killed when moribund; the other 4 survived 5 to 12 days (Table).

The two 6,000 r monkeys which lived 12 days developed alopecia of the scalp and face and ulcerations of the face and mouth. They showed a gradual return of appetite and activity until a day before death, when they again became depressed and their condition declined rapidly.

Neurological Observations.—During the first three days poor coordination, loss of the pupillary light reflex, and myoclonic twitches and seizures, both tonic and clonic, were observed. Blindness, as judged by failure to avoid obstacles or fix upon moving objects, occurred in four monkeys. No opacities of the media were noted upon ophthalmoscopic examination, although in one monkey which was not blind, anterior-chamber hemorrhages appeared. The blind monkeys, as well as two others, had completely dilated pupils, which did not react to light. The remaining 10 animals had no apparent visual disorders.

When undisturbed, the animals shivered constantly; rectal temperatures at this time were dropping rapidly to subnormal levels. Handling of the monkeys often appeared to precipitate coarse repetitive jerks involving the whole body. Six monkeys of this group were subject to repeated seizures during the first three days following irradiation. These seizures were variable in nature, ranging from isolated choreiform movements of the arms and legs to fits involving thrashing of the extremities and final stiffening of the entire body in an opisthotonic position. Nystagmus often accompanied these attacks. One animal held its head twisted far to the right and walked in circles for 12 hours preceding its death, on the second day.

Electroencephalographic Findings.—Preirradiation tracings of all monkeys of this series, as of those studied by Eldred and Trowbridge,[3] consisted predominantly

of regular 7-11 per second waves of low medium amplitude (20-50 μv) (Fig. 2*A*). Superimposed on this alpha rhythm, and at times replacing it, was very low amplitude, 15-20 per second activity.

Diffuse electroencephalographic abnormalities were observed in all animals after 6,000 and 4,500 r irradiation. The major changes included periodic spiking, seizure patterns, and a generalized slowing of the activity, together with an increase in ampli-

Exposure, Dosage and Survival Time

Monkey No.	Weight, in Kg.	Sex	Dose of X-Rays, r	Time of Death After Irradiation
A- 1	3.2	F	6,000	48 hr.
A- 2	2.2	F	6,000	55 hr.
A- 3	2.4	F	6,000	12 days
A- 4	3.7	F	6,000	52 hr.
A- 5	3.3	F	6,000	36 hr.
A- 6	2.3	F	6,000	12 days
A-26	2.6	M	6,000	18 hr.
A-30	2.8	F	6,000	32 hr.
A-31	3.2	F	6,000	16 hr.
A-32	2.7	F	6,000	8 hr.
A-39	2.8	F	6,000	36 hr.
A-33	3.0	M	4,500	10 days *
A-34	2.5	F	4,500	6 hr.
A-35	2.3	F	4,500	21 hr.
A-38	2.5	F	4,500	5 days *
A-40	2.5	F	4,500	34 hr.*
A-11	2.1	F	3,000	18 days
A-12	2.0	F	3,000	18 days
A-13	2.1	F	3,000	21 days *
A-14	1.7	F	3,000	17 days
A-15	2.1	F	3,000	16 days
A-16	1.7	F	3,000	15 days
A-36	2.6	M	3,000	5 days *
A-37	2.3	F	3,000	29 hr.
A-41	2.5	F	3,000	36 hr.*
A-27	3.1	F	2,000	7 days *
A-28	3.1	F	2,000	9 days
A-29	3.2	F	2,000	3 days *
A-17	2.5	F	1,500	4 mo.*
A-18	2.4	F	1,500	4 mo.
A-19	3.5	F	1,500	8 mo.
A-20	2.4	F	1,500	6 mo.*
A-21	3.6	M	1,500	6 mo.*
A-22	2.5	F	1,500	5 mo.*
A-23	2.6	F	1,500	3 days *
A-24	3.0	F	1,500	12 days *
A-25	2.1	F	1,500	6 days *

* Animal killed. Other animals succumbed spontaneously or were killed when moribund.

tude. The last change was seen as early as four hours after irradiation in two animals, but in most cases appeared later within the first day (Fig. 2*B*). At 48 hours the activity was even slower (3-4 a second) and had an amplitude of up to 200 μv (Fig. 2*C*). Occasional spiking, occurring simultaneously in all leads, was seen in 11 animals.

Seizures were recorded in three animals 4 to 21 hours after irradiation. In two monkeys these were subclinical seizures, lasting 5-10 seconds and consisting of regular, very high amplitude waves of 8 per second frequency. In one of these animals the seizures could be precipitated by loud click stimuli, indicating a lowered convul-

sive threshold. In the third monkey an EEG record was obtained during an overt seizure. This tracing showed generalized preliminary spiking, which increased in amplitude and frequency until the record, especially in the left parietal area, had the high voltage (to 500 μv) and rapid (30 a second) spike activity that is typical of a grand mal seizure (Fig. 3*A*). This abnormality in the EEG began while the monkey was quiet and continued until it was obscured by the muscle artifacts of an overt seizure, lasting several minutes. A tracing taken one hour later showed 2-3 per second, high amplitude waves, together with occasional spiking in all leads (Fig. 3*B*).

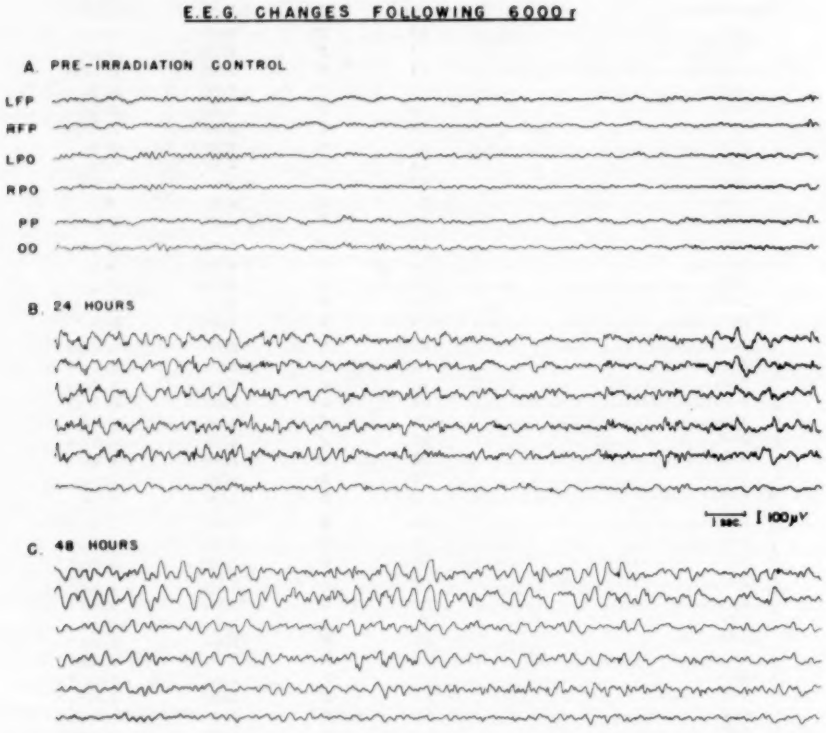

Fig. 2.—Control preirradiation tracing (*A*) and records showing EEG changes one day (B) and two days (*C*) after 6,000 r to the head. In all records, abbreviations are as follows: *LFP* and *RFP*, left and right frontoparietal leads; *LPO* and *RPO*, left and right parieto-occipital leads, and *PP* and *OO*, transparietal and transoccipital leads, respectively.

The EEG tracings of animals living into the second week were dominated by high amplitude waves of 2-4 a second frequency with bursts of 7-9 a second waves and occasional spiking.

3,000 r

General Observations.—Although most animals in this group lived about three weeks (Table), they did not develop symptoms of systemic radiation sickness. Initial anorexia was absent, and body weights remained constant until about a week before death. General behavior seemed unchanged for 10 days, but then the activity of the

monkeys gradually diminished. At this time, multiple ulcerations appeared in and around the mouth, on the cheeks, and around the ears. These ulcerations progressed to the extent that the animals could not eat, thus indirectly contributing to their deaths.

Neurological Observations.—The early neurological findings in this group were similar to those of the 6,000 and 4,500 r monkeys. Coarse jerking was again observed, although it did not become prominent until the third or fourth day, whereas in the 6,000 r group it was noted within 24 hours. Seizures, associated with opisthotonos and nystagmus and involving all extremities, were seen in two animals at 9 and 30 hours respectively. Three animals showed loss of the pupillary reflex to light, but none became blind.

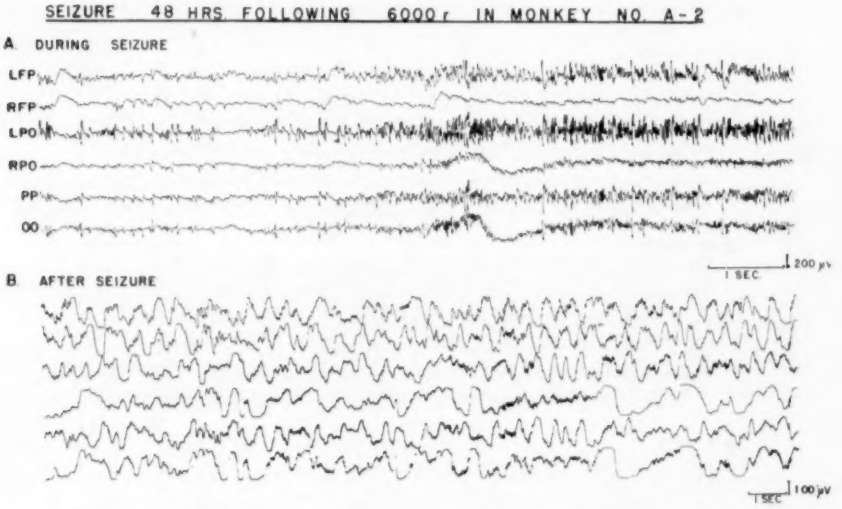

Fig. 3.—Records showing onset of seizure two days after 6,000 r to head (*A*). Animal was quiet at this time, but an overt grand mal seizure appeared shortly. Record *B* was taken one hour later.

Several new abnormalities were noted in the 3,000 r group during the second week. A tremor having a frequency of about 6-8 a second appeared and although present at rest, increased during intentional activity. The tremor occurred primarily in the limbs and thus differed from the shivering seen in the more heavily irradiated monkeys. Patellar and, to a less degree, bicipital reflexes were exaggerated in all monkeys. Three animals developed spastic paralysis of the lower extremities during the third week, and one of these also exhibited unilateral facial paralysis.

Electroencephalographic Findings.—The EEG tracings of animals in the 3,000 r series showed no changes at six hours (Fig. 4*A*), the first abnormalities being noted at about 24 hours, when 3-5 per second activity of medium to high amplitude became predominant (Fig. 4*B*). This activity then slowed still further to about 2-4 waves a second, which persisted until the death of the animal (Fig. 4*C*, *D*, and *E*). In one monkey the slow 2-4 per second waves were interrupted by an overt grand-mal seizure, which was followed by an essentially isoelectric tracing in the postital period.

The routine dose of pentobarbital was found to cause deeper anesthesia after irradiation than before (Fig. 5*A* and *B*). This increased sensitivity was progressive, and at 7 to 9 days very deep levels of anesthesia were seen (Fig. 5*C*), characterized by the appearance of "black-outs" in the EEG tracings.[18]

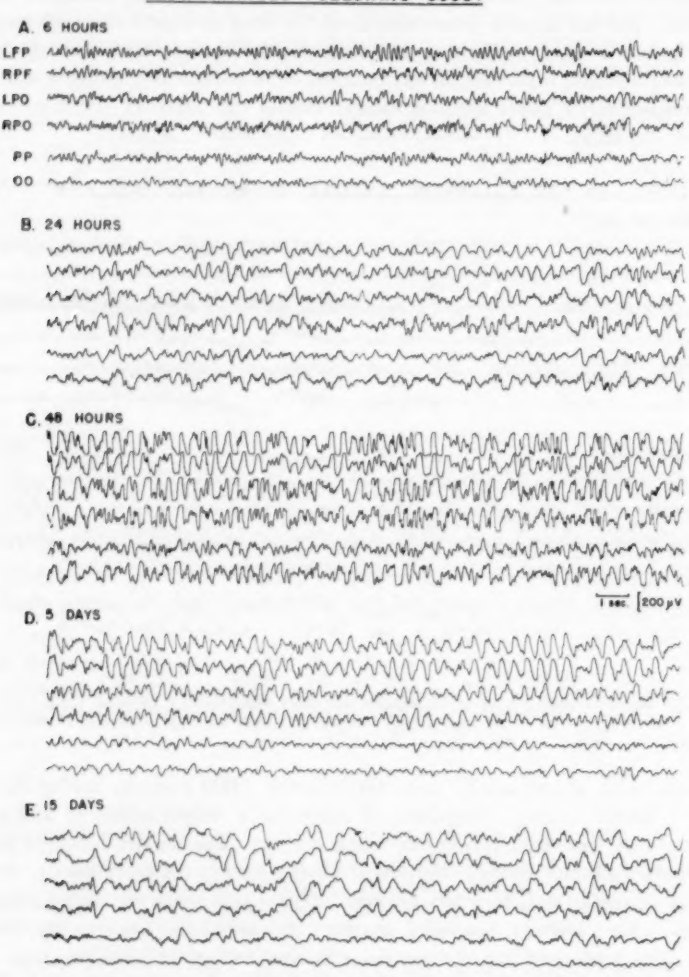

Fig. 4.—Serial records showing characteristic EEG changes following 3,000 r to the head.

2,000 AND 1,500 R

General Observations.—In this group, anorexia and other changes of behavior were not noted until the beginning of the second week, when the animals began to eat less and strength and activity were concurrently decreased. Mucous membranes of the eyes, nose, and mouth became coated with glairy, nonpurulent secretions, and

extensive facial ulcerations developed. By the end of the third week, the animals had lost 17 to 35% of their body weight. General improvement was noted in the fourth week; and at two months, the ulcerations were healed, activity and strength were again normal, and body weights had returned to preirradiation levels. The six animals which were allowed to survive continued in good health until they were killed, four to eight months later.

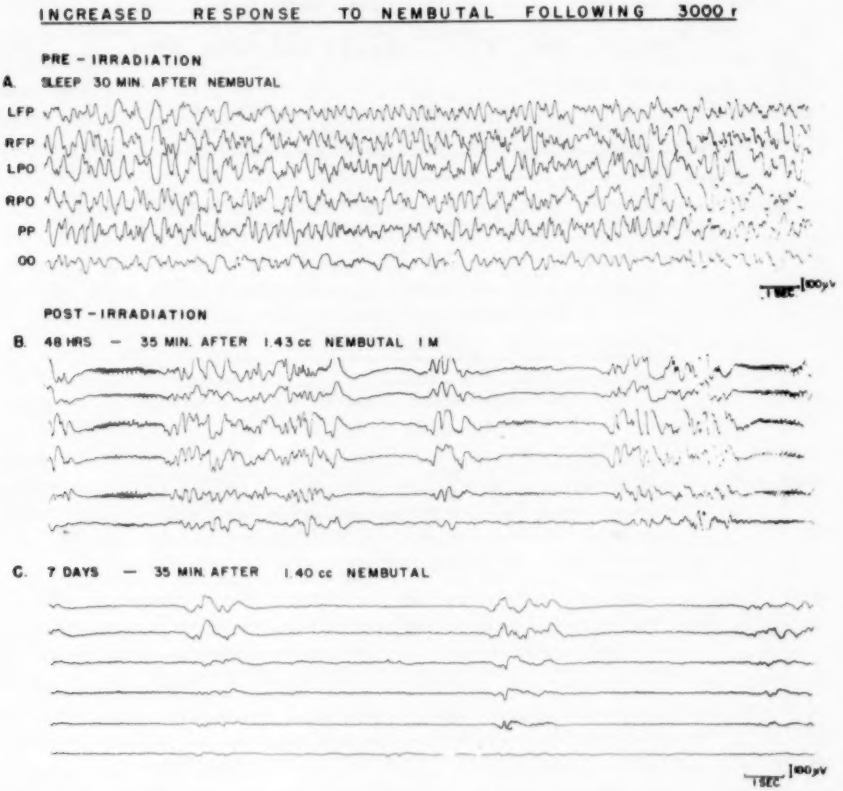

Fig. 5.—EEG tracings before (*A*) and two days (*B*) and 7 days (*C*) after 3,000 r to the head, showing the increased susceptibility to Nembutal anesthesia. All records were taken 30-35 minutes after intramuscular injection of pentobarbital (35 mg. per kilogram).

Neurological Observations.—Few neurological signs were observed in this group. In two monkeys poorly coordinated limb movements were noted toward the end of the first week, and in two others nonintentional tremors appeared during the second and third weeks. The eyes of the 1,500 r animals showed no changes, but, of the three receiving 2,000 r, two became blind and all had loss of the light reflex. Four to six months following irradiation, occasional grand-mal seizures were seen in two of the six surviving 1,500 r animals. No other neurological abnormalities were observed in later months.

Electroencephalographic Findings.—On the day following irradiation the normal alpha activity in four of the animals was frequently interrupted by runs of 3-5 per second, high amplitude waves (Fig. 6*A* and *B*), and by the fourth day such slow activity characterized the tracings of all the animals (Fig. 6*C*). On the ninth day the tracings of half the monkeys were returning to normal (Fig. 6*D*). In two animals, however, focal abnormalities consisting of periods of regular, high-voltage, 12 per second waves were seen at this time in the right occipital and left parietal leads,

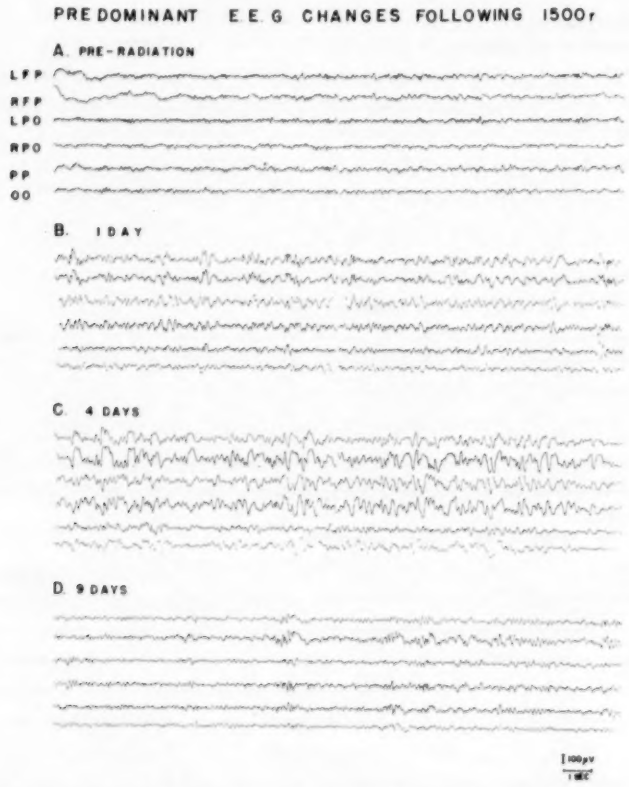

Fig. 6.—Serial records showing characteristic EEG changes folowing 1,500 r to the head.

respectively. At the 16th day only one EEG was distinguishable from its preirradiation control, and all subsequent records appeared normal until the third month.

At three months focal abnormalities consisting either of continuous, very slow activity or of bursts of fast, high amplitude waves were observed in five monkeys. On one occasion the sixth monkey of this group developed a spike-dome pattern in all leads involving the right hemisphere. The remainder of these EEG's and all other tracings taken at two to six months showed 7-9 per second rhythm of rather low amplitude (10-20 μv).

OTHER OBSERVATIONS

Temperature.—Rectal temperature readings were taken in 19 animals at 4 hours, 24 hours, and daily thereafter. In all groups the body temperature rose 1-3 degrees (C.) by the fourth hour, decreasing again to control values at 24 hours. The temperatures of the 6,000 r animals dropped rapidly to subnormal levels during the second day.

Blood.—The prolonged depression of blood elements, which is characteristic of the total-body radiation syndrome, was not seen in the present animals. Within one day the circulating lymphocytes dropped sharply, a reflection either of stress or the well-known lympholytic action of x-rays. At the same time the neutrophile count rose, resulting in a net elevation of the total white cell count. Within four days the blood cell counts in most cases returned to the control levels, where they remained except for preterminal changes. Erythrocyte and platelet counts were essentially unaffected.

Autopsy.—Except for the above-mentioned lesions of the facial skin and mucous membranes, no gross abnormalities were found in organs other than the brain. Early increased intracranial pressure was indicated in the 4,500 and 6,000 r group by obliteration of sulci, by the presence of a pressure cone at the foramen magnum, and by the fact that the cortex bulged through the incised dura. This edema had greatly subsided in those animals which were autopsied in the second week. The brains of the 3,000 r animals killed at three to six days showed slight to moderate edema, which, however, had almost completely disappeared in those monkeys dying after the first week. Edema was not observed grossly after 2,000 and 1,500 r irradiation. In the most heavily irradiated group, small hemorrhages appeared over the frontal and occipital cortices in one monkey and over the pons in another. No other gross indications of intracranial hemorrhage were noted.

COMMENT

The micropathological changes in the brains of the animals studied in these experiments are to be reported in a separate paper,[17] but since these findings are pertinent to the present discussion they are briefly summarized here. The changes in the brain during the acute period consisted of injury to neuronal and neuroglial elements, and of alterations in capillary permeability, as evidenced by severe edema, leucocytic infiltration, and the passage of intravascular protein-bound trypan blue into the interstitial substance of the brain. The hypothalamus, optic chiasm, and dorsal part of the medulla oblongata were most affected, and trypan-blue staining occurred oftenest in these areas. The brains of the subacute 1,500 to 3,000 r animals, examined at two to three weeks, also showed neuronal damage but had little or no edema, inflammation, or neuroglial injury. In later months only widespread pinpoint foci of necrosis and glial scarring were found.

At the various postirradiation intervals certain correlations between the pathological changes and the functional abnormalities may be suggested. In the acute stage these abnormalities consisted of apathy and weakness, body twitching, and overt and electroencephalographic seizures of the grand-mal type, together with early replacement of the normal alpha rhythm by slow waves of high amplitude. The relevant causal factors here appear to be the increased intracranial pressure with edema and inflammation, the neuronal damage, and perhaps the toxemia accompany-

ing tissue breakdown. The sudden loss of temperature regulation and the onset of blindness might be related to the fact that pathological changes were especially severe in the hypothalamus and optic chiasm. Herniation of the brain through the foramen magnum, seen at autopsy in each of the 12 monkeys dying between 6 and 55 hours, may have been a major factor in the deaths of these animals.

In the subacute stage behavioral changes usually did not begin until at least 10 days after irradiation, when a lessening of activity and strength appeared, to be followed in the 3,000 r animals by tremor of the extremities, exaggerated reflexes and, in several animals, paralyses. The EEG recordings were characterized by slow waves of high amplitude, an abnormality which usually commenced late in the first day. Although ulcerations of the scalp and mouth, and the resultant difficulties with eating, were complicating factors, these were changes that did not become severe until late in the third week and could not have been the primary cause of the neurological abnormalities. Most probably the latter were a direct result of the widespread neuronal degeneration that was seen in the brains during this period, although the mere absence of edema does not eliminate the possibility that continued changes in the metabolic environment of the neurons may have been contributory. The seven deaths occurring between the 12th and 18th days possibly resulted from the severe damage of vital medullary and hypothalamic areas, for none of these animals showed signs of increased intracranial pressure at autopsy.

In later months, each of the six surviving monkeys (1,500 r) on at least one occasion demonstrated focal abnormalities in the EEG recording, and two animals had overt seizures. Presumably, these abnormalities were related to the presence of widespread miliary scarring of the brain.

Particularly noteworthy has been the absence of the vomiting, diarrhea, and hemorrhages which are so commonly associated with radiation sickness. The fact that these signs are absent in head-irradiated animals having extensive brain damage, whereas they are severe in total-body irradiated monkeys (600-800 r) with no specific involvement of the nervous system,[8] leads to the conclusion that no causal relationship exists between the injury produced in the central nervous system by irradiation and these symptoms of radiation sickness.

The threshold for the appearance of signs of injury to the nervous system of the monkey seems to be about 1,500 r given as a single exposure. As this amount of x-radiation to the whole body would lead to 100% mortality,[8] it is evident that the prognosis is unfavorable if specific EEG or neurological signs appear after total-body exposure of the monkey to ionizing radiation. When the head alone is irradiated, it appears that survival is possible only if the dose is less than 2,000 r. Damage to the brains of these survivors may be insufficient to reveal itself in later months despite earlier transient presence of EEG and neurological abnormalities. In other cases there may be focal abnormalities in the electroencephalogram.

SUMMARY

The heads of 37 monkeys were subjected to single exposures of x-radiation at 6,000, 4,500, 3,000, 2,000, or 1,500 r. Electroencephalograms and neurological examinations were made over periods as long as eight months after irradiation, and pathological changes were studied terminally.

Radiation sickness as manifested by the usual gastrointestinal and hematological signs was not encountered.

In addition to a general depression of activity, blindness, opisthotonic and grand mal tonic and clonic seizures, ataxia, tremors, paraplegia, and partial facial paralysis were observed.

Early EEG abnormalities consisted of a slowing of activity, with an increase in amplitude; spiking and grand mal seizure patterns occurred. In later months survivors (1,500 r) developed focal abnormalities.

The relation of the neurological and electroencephalographic abnormalities to the pathological findings is discussed. Microscopic aspects of the pathological changes are described more fully in an accompanying paper.[17]

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Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Raymond D. Adams, M.D., President, Presiding

Regular Meeting, March 19, 1953

Sensory Disorders in Cerebral Palsy, with Moving Pictures. DR. BRONSON CROTHERS.

At the Children's Hospital we are recalling patients who have been seen at the hospital for cerebral palsy. We have limited the material to patients known to Dr. Randolph K. Byers or to me.

The response to personal letters has been more satisfactory than we expected, and most of the patients who are within reach have come back cheerfully. Of course, we have failed to find many, and many have given up and retired to custodial institutions.

With all the difficulties, we have good follow-up histories on some 400 and have adequate contact with at least one-half of these.

An interim report on this material would be confusing if we tried to cover all possible points, but we may suggest certain methods.

The material we are reviewing consists of clinical records, which are often very brief but for which Dr. Byers and I are fully responsible, a considerable number of pneumoencephalograms, and a mass of moving pictures. In recent years we have a fair number of electroencephalograms. Perhaps of equal value with the sum of the aforementioned is a file of psychological reports, all done under the supervision of Dr. Edith Meyers and her single predecessor, Dr. Elizabeth Lord. A single physical therapist, Miss Mary Trainor, has directed training.

The reexamination of these patients is, of course, disconcerting. The usual patient had been examined in infancy or very early childhood. Sensory study was rarely attempted. This error was at once apparent when adult patients appeared for review. Dr. J. P. M. Tizard, fresh from Queen Square, began to point out that astereognosis and hemianopsia were present in almost half our hemiplegics.

The discussion on this point is due entirely to his initial stimulus. What we have done is to supplement our follow-up study of older patients by collecting a series of young children.

The attempt to show on film the method of study is presented for discussion.

Significance of Tonic Neck Reflexes in Infancy and Childhood. DR. RANDOLPH K. BYERS.

Motility in mammals was divided by Magnus and his students into principal and voluntary motility. Principal motility was defined as the motility of posture, largely implemented by reflexes of one part of the body affecting other parts of the body. Prominent among these reflexes were the tonic neck reflexes, which affected paired extremities, either right and left or fore and hind. With the face turned to the right, the right arm and leg went into extension and the left into flexion; with the face to the left, the extremities reversed their posture. With the neck extended, the forelimbs went into extension and the hind limbs into flexion; with the head flexed, the forelimbs flexed and the hind limbs extended. Tonic neck reflexes were seen in their pure form in laboratory animals in which the brain stem was transected just above the entrance of the eighth cranial nerves and in whom both labyrinths had been destroyed. They were seen frequently in the motility of intact quadrupeds from amphibia to mammals with a few exceptions, but never in the activity of adult bipeds. Intact apes and human beings showed them in the early months of infancy, but as the upright posture was assumed, they tended to be automatically suppressed. In human infants they affected the arms more than the legs, and were easily suppressed by such activities as crying, struggling, and the like. On casual inspection they were seldom seen after about 4 months of age, though on continuous cinematographic survey they were occasionally seen until the eighth or ninth month of life.

After the middle of the first year of life tonic neck reflexes were always pathological. In acute disease they were seen in relation to various severe encephalopathies, and follow-up studies

in a few cases have always shown more or less residual cerebral damage. Chronically present tonic neck reflexes were an important finding in cerebral palsy. In many instances severe intellectual defects were also present. In a few children with cerebral palsy fair to good intellectual capacity might appear in the presence of tonic neck reflexes. Tonic neck reflexes might be seen in cerebral palsy, in which the motor signs were either pyramidal or extrapyramidal. In all persons severe postural difficulties were evident, and only a very few were able to stand, and very few to walk unassisted. A few intellectually able children were able to work out special motor capacities, such as playing cards, using a sewing machine, ironing with the feet, or writing with the mouth. In a few instances tonic neck reflexes were utilized voluntarily by the patients for dressing and undressing. Authoritative measures of a physical therapeutic nature were helpful in a functional sense to almost no children with tonic neck reflexes, and were a distinct handicap to the resourceful few.

CONCLUSIONS

Tonic neck reflexes occurring after the middle of the first year of life were an evidence of either acute or chronic impairment of the motor apparatus of the cerebral hemispheres.

Ingenious children who exhibited tonic neck reflexes might be able to incorporate them into their voluntary activity, thus tending to blur the distinction between principal and voluntary motility set up by Magnus.

Voluntary activity in children and adults showing tonic neck reflexes was always very slow and noncompetitive in nature.

These points were illustrated with slides and motion pictures.

DISCUSSION

DR. RAYMOND D. ADAMS: We do not have too much idea of the kind of disease that is being dealt with. This makes it difficult to say what can be expected from a disease now and in the future. However, some people might not agree about the disease process.

Another problem is to assess the status of the nervous system at any time during development. I wonder if it would not be possible to take the methods of examination used in older children and carry them back to the younger children, thus allowing defects to be found earlier in life and predictions to be made.

DR. CLEMENS E. BENDA: I should like to ask in which way Dr. Crothers' and Dr. Meyers' observations agree with the psychological observations of Goldstein, Werner, and Strauss on the brain-injured child, which they published in several papers. They pointed to the great amount of perceptual defects which can be found in the brain-injured child, and they used their observation for distinguishing between the brain-injured child and feebleminded children of other types.

I do not share Dr. Adams' skepticism in regard to our knowledge or ignorance of the conditions of cerebral palsy. My autopsy material of cerebral palsy due to brain injury exceeds 65 cases in which a complete study of the brain and nervous system has been made. The choreoathetosis in the cases of so-called "athetoid" cerebral palsy is usually associated with status marmoratus of the basal ganglia, and I have not seen a single case of the pyramidal-extrapyramidal type of cerebral palsy in which a status marmoratus could not be found. This status marmoratus is not a congenital malformation but is a manifestation of brain injury due either to vascular pathology or to asphyxiation, as has been pointed out. In most cases of cerebral palsy, we find in the history that the child has been for days to many weeks in an oxygen tank.

DR. PAUL I. YAKOVLEV: After some years of experience with this type of patient, I have formed certain personal notions about the meaning and localization of the disorder of motility in patients with dystonia, athetosis, and similar "extrapyramidal hyperkineses." Dr. Byers has drawn attention to what I consider the cardinal feature of these syndromes when he pointed out the gross impairment of erect stance in these patients. For me the dislocation of the postural adjustments of parts of the body to the body in stance and in movements of emotional expression is the cardinal disturbance of motility in all these patients.

The motility of postural adjustment of parts of the body to the body itself, such as erect stance and all the motility of emotional expression, depends on the integrity of the nucleated derivates of the mantle zone of the neuraxis interpolated "in series" between the cortex and the final common path. It is these derivates of the mantle zone that are affected—striatum, pallidum,

thalamus, subthalamic region, and nuclei of the tegmentum. There is considerable evidence that in prenatal and early postnatal life the mantle, or nuclear, zone and its derivates are selectively vulnerable to certain types of noxae. The examples of kernicterus of the newborn and the status marmoratus are suggestive in this respect. The relative, yet consistent, sparing of the intellect in these patients is a significant corollary of a selective vulnerability of the mantle zone and of the relative resistance of the marginal zone.

DR. WILFRED BLOOMBERG: Of interest to me in this paper is our tendency to forget that these patients are not only cerebral mechanisms but also people. It seems to me in relation to modern ego psychology that these patients should give an opportunity for almost a pure culture study of hostility and of the guilt that must be generated by such hostility, on the part both of the patient and of the family. I hope studies on this problem will be undertaken.

DR. RAYMOND B. ADAMS: Your remarks show the real division between neurology and psychiatry. You are interested in the patient as a part of the whole.

DR. WILFRED BLOOMBERG: We should not confuse motility with behavior. Motility is a neurologically determined pattern, but behavior is the sum total of motility plus voluntary reactions, mediated not only by neurological mechanisms and intellectual wish but by emotional drive. In considering any split in the approach between the neurological and the psychiatric, we should remember this and fuse the two approaches.

DR. BRONSON CROTHERS: This presentation was planned to be a demonstration of the method of recording the life of a patient in moving pictures, and, of course, we have just started. I realize that any discussion would go far afield, and there is no question that the discussion has been pretty wide-flung.

A detailed answer to all the questions asked would cover a great deal of ground, but I should say that, with the help of psychologists, we have all been pretty well indoctrinated with the work of Dr. Strauss, Dr. Goldstein, and the others who have been interested in the psychological deviations.

Dr. Adams brings up the perennial question as to whether it is possible to improve examinations of very young children. I should think our impression is that examination of babies requires a good deal more sheer observation and a great deal less elaborate technique than similar studies in adults; but of course it is obvious that we have not begun to get the best possible tools.

I should like to defend the term "cerebral palsy." Admittedly, it means nothing very definite, but there is a general agreement that a child with cerebral palsy is not suffering from active cerebral disease. Therefore the emphasis can properly be left on the physiological and psychological deviations.

So far as the psychiatric study of these children goes, it is quite evident that a survey of this kind has to be conducted with great discretion. It is evident enough that hostility and frustration are common. The evidence of this pours out; yet when we are seeing the patient only once, it is perhaps permissible to record what comes, rather than to search too vigorously for elaborate difficulties.

DR. EDITH MEYERS: In answer to Dr. Bloomberg's remarks, we have evidently a cross section of the population and find the most interesting variety of attitudes. It is fascinating to observe what the same, or at least a similar, problem means in different families and in different settings. It also is particularly interesting to see what the same problem looks like at different phases of the child's and of the mother's development. For many mothers it is easiest to take when the baby is still young and does not have to compete with others. Many mothers are relieved to know that disease was an unavoidable accident, and not something due to their having done badly. There are innumerable important and interesting angles in this group concerning the interactions of families and patients. When we study these patients in the limited time allotted, our main problem is how not to stir them up or to start problems which we cannot finish and which will leave them unhappier than they were.

In answer to Dr. Benda, it would take a whole evening to talk intelligently about the problems of irregularities of function and the methods of detecting them. There is much more to the so-called perceptual-motor problems; rough detection is just the beginning. We are interested from the psychological and theoretical angles in determining how such distortions develop and what they mean at different age levels. Dr. Werner and Dr. Goldstein have been pioneers. We

are trying to go on from there. Strauss's work is only a beginning. He describes a very heterogenous group and is extremely interesting, but we have to go beyond this. Differentiation of various groups has just begun. In general, we find that patients with extrapyramidal disease show less of the perceptual-motor difficulties, but only if they have the pure extrapyramidal type. There are all kinds of degrees.

Psychological follow-up studies on old patients with cerebral palsy were made to evaluate the patient's general competence and adjustment to life situations. A large number of patients with acquired hemiplegia and a smaller number with mixed types of cerebral palsy were investigated. The over-all results are sobering. Many patients are seriously impaired in their ability to function in a community; many are mentally defective or dull; very few are fully competitive, and only a handful carry responsible positions. Even the most competent ones live lonely and socially restricted lives. Prolonged dependence on authoritarian figures (parents; doctors; therapists) creates special problems in personality development.

The most successful and happiest patients were those who found methods to circumvent their disability through their own efforts. Self-motivated activities and a wide scope of over-all experiences proved more beneficial than intensive individual therapy. Exaggerated expectations lead to unhealthy pressure and disappointment. The need for realistic attitudes and the acceptance of family attitudes for young patients and a plan for organized group living for adult patients is apparent.

CHICAGO NEUROLOGICAL SOCIETY

Douglas N. Buchanan, M.D., *President*

Meyer Brown, M.D., *Vice-President*

Leo A. Kaplan, M.D., *Secretary*

Regular Meeting, Oct. 13, 1953

Obituary: Dr. Frederick Hiller. DR. ERIC LIEBERT.

Cerebral Air Embolism Following Attempted Abortion: Report of a Case. DR. ERNST HAASE.

A young woman, pregnant in her third month, had her husband insert a patent plastic tube into her cervix and blow air into her uterus. When she experienced a sharp pain in her right shoulder, he gave up, but six days later tried again, this time blowing with full force. Suddenly she complained of severe pain in her chest, turned blue, went into opisthotonos, and was unresponsive and dyspneic. After artificial respiration color and breathing returned to normal, but the patient remained in semiconscious state, with restlessness, agitation, and extreme hypersensitivity to touch, followed by fever, vomiting, and incontinence. Neurologically, there was stiffness of the neck, a positive Kernig sign, paresis of the right arm, a Babinski sign on the right, and motor and sensory aphasia. Complete recovery followed within five days, with retrograde amnesia, and the pregnancy was preserved.

It must be assumed that the forcefully blown-in air entered open sinuses within the pregnant uterus, which was probably already injured by the first manipulation, and ascended to the brain through an open foramen ovale, invading mainly the subarachnoidal spaces and the left Sylvian artery. A gradual absorption of the air bubbles may have accounted for the good recovery.

DISCUSSION

DR. IRVING C. SHERMAN: I wonder how Dr. Haase interpreted the first symptom, of pain in the shoulder.

DR. ERNST HAASE: I believe that some air went through the tubes, as occurs in Rubin's test for patency of the tubes.

DR. ROLAND P. MACKAY: This very interesting case recalls one that came to my attention years ago in Germany, in which I studied the brain of a nurse who had died suddenly, after an injection of soft soap into the uterus to produce abortion. There were vascular changes, poor staining of the cells, and incomplete softening in many places, so that we felt there were

multiple emboli. In experiments on animals soft soap was injected into the blood stream, with the result that the sodium and potassium soaps were converted into insoluble calcium soaps, producing multiple emboli not only in the lung but in the brain.

I would like to ask Dr. Haase whether his patient actually had a patent foramen ovale to account for the air embolism.

DR. ERNST HAASE: A patent foramen ovale could not be demonstrated; its presence could only be concluded from the clinical course. In those cases in which air was found at autopsy in cerebral vessels after attempted abortion (Jürg im Obersteg), an open foramen ovale was always present. In our case it could be argued that the patient had suffered only a pulmonary embolism, and that the long period of dyspnea and cyanosis resulted in general cerebral anoxemia. However, the localizing neurological signs pointing to a focus in the left hemisphere and the modus of recovery make the diagnosis of cerebral air emoblism very likely.

Three similar cases are described by Digonnet and his co-workers, with the same clinical picture of agitated coma, extreme sensitivity to touch, and some neurological deficit, which also ended in recovery, with the pregnancy preserved.

Maternal Obstetrical Paralysis: Report of a Case. DR. HAROLD M. MANFREDI.

The case reported was that of a 27-year-old Negro woman who developed bilateral obturator and lumbosacral cord (anterior division of L 4-5) neuropathy after delivery of her third child. The two previous pregnancies terminated in normal spontaneous deliveries. Although the patient's pelvic measurements were borderline normal, a dystocia occurred because of the large size of the baby, and delivery was further complicated by brow presentation, which necessitated rotation and forceps delivery. Eight months after delivery the neurological examination was negative, except for unilateral "peroneal palsy." The drop foot and inability to dorsiflex the toes, along with patches of analgesia in the dorsum of the foot, are the commonest residuals in the cases reported in the literature. The lumbosacral cord is the most vulnerable of all pelvic nerve tissue, as it crosses the pelvic inlet and receives the greatest trauma in delivery. These fibers terminated principally in the common peroneal nerve, accounting for the peroneal palsy. This explanation seems more reasonable than those previously suggested in the English literature.

DISCUSSION

DR. ALEX J. ARIEFF: I wonder whether the use of spinal anesthesia could be a factor.

DR. DOUGLAS N. BUCHANAN: I am not sure of the time limit between the delivery of the baby and the onset of the paralysis.

DR. HAROLD M. MANFREDI: With regard to Dr. Arieff's question: Two spinal punctures were performed shortly after onset of the palsy, and no pleocytosis or other abnormality was found, indicating to me that anesthesia was not an etiologic factor.

In answer to Dr. Buchanan, there were three days between delivery of the baby and onset of the paralysis as reported by the patient; however, it must be noted that the patient was in poor medical condition immediately post partum and she was unable properly to evaluate her status until she rallied sufficiently.

Current Concepts of Military Neurosurgery. COLONEL JOHN MARTIN, Medical Corps, United States Army.

The essential differences between military and civilian neurosurgery are minimal, those differences which do exist being due to such factors as the actual location of the hospital, restrictions imposed by law upon military medical practice, and the availability of physicians of varying degrees of experience for the performance of surgery during times of war. A large segment of military neurosurgery is made of patients suffering trauma to the nervous system, but there is also a high incidence of work concerned with tumors, intractable pain, herniated nucleus pulposus, and pediatric surgery. The principles of surgery in these various conditions do not vary in military practice from those of civilian practice, but certain rules do prohibit surgery in the Army and the Air Force when the condition existed prior to service. The armed forces are faced with the problem of trying to rehabilitate patients who may be very badly motivated for any type of military service and who are, from the beginning of their term of service,

emotionally and physically poorly adapted to such service. Certain specific surgical procedures are discussed in the light of their efficacy in the military neurosurgical case. It is also pointed out that military neurosurgery is currently concerned with the training of neurosurgeons for the Army and Air Force, in an accredited program in which clinical material, adequate supervision, and provision for investigative studies all are available.

DISCUSSION

DR. HAROLD C. VORIS: During the last four years, I have been the neurosurgical consultant to Percy Jones Hospital, Battle Creek, and I have had occasion to make many trips up there. I can testify to what Dr. Martin has said.

As Dr. Martin said, not only are the facilities as good as, or better than, in a civilian hospital, but there is a fine spirit of coordination among the various departments. I can also say that many battle casualties were returned from Korea whose treatment received overseas, I can honestly say, was very good. Dr. Martin, of course, put his finger on one of the bad phases of Army surgery, that is, the lack of ability to follow up the cases adequately. That is a serious deficit from the standpoint of the individual surgeon.

An interesting thing up there in the past year or so is the change in policy in the Army toward personnel with convulsive seizures. That would be of interest to some members of the society. Dr. Martin can probably give more details about that than I.

The Spinal Cord-Injured Patient of the Korean War Period: Results of Applications of Principles of Management Derived from World War II Studies. BENJAMIN BOSHES, M.D.; ELI L. TIGAY, M.D., and ISRAEL ZIVIN, M.D.

Since World War II this group has been studying the natural history of the reflex activities, spasms, pain, recovery of function, and complications after lesions of the spinal cord and has published reports on its findings.

The Korean war and concomitant civilian injuries accumulated at this center have presented an opportunity for the practical application of the principles derived from the observations.

In a study of 100 recent cases, military and civilian, it is possible to state that the recent patients have benefited directly from the acquired knowledge. Their nutritional state is better; they have fewer and smaller decubiti, fewer renal and bladder stones, fewer genitourinary infections. This, in turn, means more rapid return of neural function in the autonomic or partially isolated distal portion of the spinal cord. The recognition of the progressive decrease in pain and spasms with the passage of time has resulted in the elimination of most neurosurgical procedures and the elimination of drug and alcohol addiction.

Slides showing detailed analyses of each point are presented and comparisons made with the previously analyzed World War II material.

PHILADELPHIA PSYCHIATRIC SOCIETY

Frederick Kramer, M.D., President, in the Chair
Regular Meeting, Oct. 9, 1953

Teaching Child Guidance Concepts to Residents. DR. FREDERICK H. ALLEN.

The last three decades has seen the emergence of child psychiatry as a specialized part of general psychiatry. The impetus for this significant development has come from several sources. Psychiatry, with an increasing awareness of the importance of the early developmental period, influenced movements to develop a deeper understanding of the childhood period. The contributions of the psychoanalytic movement have had a great influence in accelerating the need to understand the child from himself rather than from the retrospective memories. Just as important was the stimulus from the community, particularly from social agencies, courts, schools, etc.

Study and treatment of the child has required the skills of several disciplines—particularly psychiatry, social work, and psychology. The pattern of the Child Guidance Clinic is built on integrating these disciplines.

Training of professional personnel has become one of the major responsibilities of our clinics. It is clear that special training for all three disciplines is essential.

The training program of the Philadelphia Child Guidance Clinic was discussed as an example of what constitutes a well-recognized training center. This program has been built on three interrelated parts—clinical experience, supervision by trained child psychiatrists, and seminars on basic principles that form the foundation of the professional development of the psychiatrist.

Teaching Child Psychiatry Concepts to Residents. Dr. Earl A. Loomis Jr., Pittsburgh.

In providing large portions of the training of psychiatrists, child psychiatrists, and pediatricians, our responsibility is to purvey content and a point of view. We hope to develop researchers, teachers, clinicians; at the very least, better practitioners of comprehensive medicine, psychiatry, and pediatrics.

The experience, knowledge, and personality of the teachers must be translated into communicable currency which can be absorbed and adapted by the residents. Provided experience should include individual and group supervision and interdisciplinary collaboration.

Residents should be selected with a view to their background and their capacity to integrate the training into their over-all plans. The program for a pediatrician may differ considerably from that for a child psychiatrist-to-be. Residents are physicians in graduate training who must wield the responsibility appropriate to their position. Morale is preserved by safeguarding their dignity. Participation in varying interdisciplinary functions gives understanding of the particular talents of other disciplines.

Content includes psychopathology of the child, the family, and the culture; agencies and institutions; psychological testing techniques; experiences in group and action techniques, including sociometry and psychodrama, and personal psychonanalysis and didactic instruction in psychoanalysis.

Experiences should include well-baby and well-child clinics; nursery and elementary schools; child guidance centers; children's hospitals, and children's residential treatment services.

Obituaries

FREDERICK HILLER, M.D.
1891-1953

Dr. Frederick Hiller died suddenly in his home in Evanston, Ill., on June 28, 1953, at the age of 62 years.

His death was unexpected and occurred at a time when he was ready to leave the country for an extended European trip to attend the International Neurological Congress in Lisbon, and the meeting of the German Neurological Society in Munich in the fall of 1953.

Frederick Hiller was born April 20, 1891, in Zittau in Saxony, Germany, the son of Karl Gustav and Berta Freund Hiller. He received his early education in Zittau and began his medical career in 1910. He studied at the Universities of Munich, Rostock, Berlin, Freiburg, and Leipzig, and he received his degree of Doctor of Medicine from the University of Munich in 1917 with a magna cum laude dissertation on "The Treatment of Abdominal Wounds in the War." Dr. Hiller started his specialized education in neurology and psychiatry in Munich. He became assistant to Spielmeyer in 1922 and assistant at the Neurological Clinic in Munich in 1923. In 1927 he received the title of Privatdozent at the same university on the basis of a thesis on "The Connections of Degenerative Changes of the Central Nervous System to Its Content of Fat and Ester Splitting Enzymes." In the same year Dr. Hiller came to Chicago as an associate professor in neurology at the University of Chicago, where he remained until 1929. On his return to Munich he became professor of neurology at the University of Munich. In 1938, he went to Geneva, Switzerland, and in 1941 he again came to the United States, having been appointed assistant professor in the department of nervous and mental diseases at Northwestern University Medical School. He became associate professor in the same department in 1948.

Dr. Hiller was a fellow and member of various medical societies, including the American Neurological Association, the Chicago Neurological Society, the Illinois Psychiatric Society, the Association of American Neuropathologists, and the German Medical Society. At the time of his death he was a member of the senior attending staff of Wesley Memorial Hospital and belonged to the courtesy staff of the Evanston and St. Francis Hospitals.

Dr. Hiller's contributions to literature were many, totaling over 50 in number. From 1926 on he paid special attention to the vascular supply of the brain and spinal cord. That year he presented a paper on "The Vascular Supply of the Central Nervous System" before the German Society of Internal Medicine, and since that time he showed continued interest in vascular lesions of the brain, culminating in his classic contribution to the Bumke and Foerster "Handbuch der Neurologie" on the "Circulatory Disturbances of the Brain and Spinal Cord," in 1936. This article is still one of the best and most extensive on this subject in the literature.

Dr. Hiller's interest and outstanding aptitude for teaching neurology is best seen in his contribution to Bergman's "Lehrbuch der inneren Medizin," for which

Presented before the Chicago Neurological Society, Oct. 13, 1953.

he wrote the chapters on the organic neurological disorders in all five editions, from 1931 to 1948. He was the author of the chapter on the diseases of the spinal cord for the German "Handbuch der inneren Medizin." All these contributions are written in an easily understood style and present an exhaustive coverage of the subjects.

During World War II Dr. Hiller was engaged in a study on peripheral nerve lesions for the Office of Scientific Research and Development. He was especially interested in the role the mesodermal tissue played in the degeneration of peripheral nerves.

Besides his many scientific contributions, Dr. Hiller carried on an extensive neurological and psychiatric practice; however, much of his time he devoted to the teaching program at the University, giving lectures in neurology and neuropathology.

In spite of all his scientific activities, Dr. Hiller found time to enjoy a rich home life with his wife, Jaqueline de Loriol, whom he married in 1931. Two daughters, Gabriele and Sylvia, were always close to his heart. Several trips to Europe and many travels in this country were enjoyed by Dr. Hiller and his family; however, he prefered a vacation on his ranch in Wyoming, where he spent his time fishing and participating in other sports, and where he could relax away from his work.

Dr. Hiller had many close friends both here and abroad, and he entertained frequently in his home in Evanston. He will be remembered and missed by all of us as a good friend and an excellent teacher who was always willing to share his vast knowledge in the neurological sciences.

ERIC LIEBERT, M.D.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

ELECTRICAL ACTIVITY OF THE CORTEX ACCOMPANYING MOVEMENT. J. A. V. BATES, J. Physiol. **113**:240, 1951.

The electroencephalograms accompanying voluntary muscular movement were recorded for five healthy subjects. A technique is described by which the sensitivity of the electroencephalogram to systematic changes in potential is appreciably increased. This technique would also permit the recording of cortical potentials preceding a movement with which they were associated, even though the subject was left to choose the instant of movement. It has been found that when alpha activity is present, there is a significant tendency for the instant of movement, as judged by the onset of activity in the electromyogram, to be related to the phase of the alpha rhythm. This finding may be consistent with others which suggest that impulses in the pyramidal tract affect the tone of skeletal muscle. It has also been possible to record 20 to 40 msec. after the onset of the electromyogram a small potential change in the region of the contralateral central sulcus. It is likely that this represents the arrival of afferent impulses from the periphery. On no occasion has this technique revealed any potential change in the cortex preceding the onset of voluntary movement.

THOMAS, Philadelphia.

STRETCH RECEPTOR DISCHARGES DURING MUSCLE CONTRACTION. C. C. HUNT AND S. W. KUFFLER, J. Physiol. **113**:298, 1951.

Responses of over 700 individual afferent fibers to stretch have been observed from various hindlimb muscles of the cat, in particular from the soleus. By their discharge patterns during contraction these afferent fibers have been classified as A and B units, according to Matthews' (1933) nomenclature. The A-receptors usually have a low threshold to stretch and cease to discharge during contraction, particularly when external muscle shortening occurs. They are thought to arise from muscle spindles. Under certain conditions the A-units may show discharges during contraction. These responses may be set up by efferent small-nerve fibers. A-units may also show responses during contraction when only larger, twitch-producing, efferent nerve fibers are excited. These responses usually occur only when the muscle is under high initial tension. Such discharges during contraction are thought to be due not to nervous activation of the muscle elements within the spindle but, rather, to tension changes on the spindle produced by the contracting extrafusal muscle fibers. It is concluded that intrafusal muscle fibers in the cat are not innervated by large motor-nerve fibers which cause the muscle twitch responses. B-type receptors usually showed a higher threshold to stretch, and their discharge rate was accelerated during contraction. They are considered to arise from tendon organs (Matthews). Conduction velocities of 200 individual stretch afferent fibers from the soleus ranged from 60 to 125 meters per second, with a peak between 90 and 110 meters per second. These correspond to the distinct large group of the afferent fiber diameter spectrum from this muscle nerve. No difference in conduction velocity between A- and B-fibers was found, indicating that impulses from both type receptors travel in fibers of similar diameter. A discharge arising from many A- and B-stretch receptors has been described, consisting of one to five impulses at high frequency occurring with brief latency after stimulation of the motor outflow to muscles. This has been termed "early discharge." Its onset may occur within 1.0 msec. after the earliest onset of the muscle action potential, and it is believed to result from early tension changes within the muscle. The role of different stretch afferent fibers in reflex function is briefly discussed.

THOMAS, Philadelphia.

EFFECTS OF DIRECT CURRENTS ON THE ELECTRICAL ACTIVITY OF THE SPINAL CORD. C. AJMONE MARSON, M. G. F. FUORTES, AND F. MAROSSERO, J. Physiol. **113**:316, 1951.

Direct currents flowing (in mammals) along a path including the spinal cord, cephalically, and the motor roots, caudally, evoke changes in the rhythmic activity of the anterior horns which are opposite for opposite directions of the current; if the cephalic electrode is negative, increase of the activity (up to synchronized tetanic hyperactivity) may follow, while flattening of the waves is observed if the cathode is caudal. These effects are similar and additive to those evoked by strychnine. The actions of the current fail or are less evident when the current is made to flow longitudinally along the cord or to follow other pathways, including other spinal and peripheral structures. It is suggested that Scheminsky's *Galvanonarkose* and *galvanischer Krampf* are fundamentally due to the direct-current excitation and inhibition of the spinal motor neurons, demonstrated by Barron and Matthews.

THOMAS, Philadelphia.

Psychiatry and Psychopathology

ON THE PSYCHOANALYTIC THEORY OF INSTINCTS. T. SZASZ, Psychoanalyt. Quart. **21**:25 (Jan.) 1952.

According to Szasz, Freud's views regarding the death instinct were influenced by the biological theories current at that time. These theories were largely based on the physics of closed systems. In an attempt to explain the nature of life processes, the principle of entropy (the second law of thermodynamics), valid for closed systems only, was extended to include organic systems. Since, however, life can occur only in open systems, the principle of entropy is not applicable under these circumstances.

The foregoing considerations were presented as the main argument against the validity of the concept of a death instinct. In addition, certain biological data were adduced in support of a unitary instinct theory. The data presented center around present-day biological theories concerning the nature of life processes. Accordingly, the hypothesis is suggested that there is but one primary instinct, a life instinct, the aim of which is to keep the life processes of a particular system in continued operation, and that this is accomplished by drawing negative entropy from the environment.

Szasz cites Carrel's tissue culture experiments (the immortal chicken heart). He believes the results of these experiments to be consistent with the unitary instinct theory proposed.

WERMUTH, Philadelphia.

BODY EGO DURING ORGASM. SYLVAN KEISER, Psychoanalyt. Quart. **21**:153 (April) 1952.

Keiser states that the concentration of libido in the functioning of the bodily orifices determines their importance in the development of the archaic body ego in infancy. Because of the preponderance of oral libido, all bodily orifices may be regarded as ingestive organs endowed with fantasies of incorporation. The orifices are of basic significance in the development of the body image, which plays a fundamental role in ego development and the sense of security about the integrity of the ego. The impaired body image in a type of oral character is delineated from the analysis of the orgastic impotence that is the result of such defective ego development. The fear of death that accompanies this type of frigidity is a mobilization of anxiety to prevent loss of the primitive ego, which threatens a total annihilation of self. Anxiety is created when destruction of the body ego is anticipated. The wish for orgasm, for postorgastic fulfillment, creates a repetitive demand, which is frustrated by the fear of the annihilation that would follow were the instinctual demand to be gratified. The orally dependent type is intolerant of tensions and seeks only to ingest and to retain the body image of the infant at the breast. Because this body image is poorly differentiated from external reality, it is threatened with dissolution by instinctual and emotional intensities. The wish to be loved (to be eaten) is equated with destruction of the body ego, which engenders anxiety that inhibits the orgasm.

WERMUTH, Philadelphia.

THE GENESIS OF ANTISOCIAL ACTING OUT IN CHILDREN AND ADULTS. ADELAIDE M. JOHNSON and S. A. SZUREK, Psychoanalyt. Quart. **21**:323 (July) 1952.

Johnson and Szurek synthesize the concepts on antisocial acting out which they have developed over the past decade. They state that their observations apply equally to the young "delinquent" and to the "psychopathic personality" of later years, who is etiologically a delinquent grown older. By means of collaborative therapy of children and parents, the authors have observed that the parents may unwittingly seduce the child into acting out the parents' own poorly integrated forbidden impulses, thereby achieving vicarious gratification. A specific superego defect in the child is seen as a duplication of a similar distortion in the organization of a parent's own personality. The outcome is doubly destructive toward the child's and the parent's ego organization unless adequate therapy of both is provided. WERMUTH, Philadelphia.

CONTRIBUTION TO THE PROBLEM OF TERMINATING PSYCHOANALYSES. EDITH WEIGERT, Psychoanalyt. Quart. **21**:465 (Oct.) 1952.

Weigert presents the countertransference as a means of determining the approaching termination of psychoanalysis. She states that the disappearance of symptoms is not always a reliable guide and that the ideal goals of mature adaptation to reality can easily become impositions of the superego, which elicit self-deception and pretense. In terminal phases of analysis the resolution of countertransference goes hand in hand with the resolution of transference.

WERMUTH, Philadelphia.

Meninges and Blood Vessels

MENINGITIS DURING GOLD THERAPY. R. M. MYERSON, J. A. M. A. **143**:1336 (Aug. 12) 1950.

The frequency of toxic reactions to gold therapy is well known. Complications involving the nervous system are perhaps the rarest of all. In an exhaustive review of the toxic effects of gold compounds, Sundelin reported cases with manifestations of involvement of the central and peripheral nervous systems. Cerebral symptoms ranged from simple depressions to frank psychoses. He also reported local nerve paralyses, herpes zoster, and polyneuritis. Leiper reported a case of polyneuritis due to gold therapy in which there was widespread flaccid paralysis of all limbs associated with an increase in protein content of the cerebrospinal fluid and pleocytosis. No cases of meningitis caused by gold have been reported.

Myerson here reports a case of meningitis occurring during the course of gold therapy for rheumatoid arthritis. Because of the temporal relations between the administration of the gold and the development of symptoms, the clinical response to dimercaprol (BAL) therapy, and the inability to establish another etiologic agent, gold must be considered as the responsible factor.

ALPERS, Philadelphia.

COARCTATION OF THE AORTA, EDITORIAL, Radiology **69**:858 (May) 1953.

The possibility of surgical correction of many congenital anomalies of the heart and great vessels has stimulated those interested in the roentgenographic diagnosis of these lesions, so that many advances have been made in the last few years.

The classic roentgenographic sign of coarctation of the aorta has long been considered to be the demonstration of notching of the under surfaces of the ribs, produced by enlargement of the intercostal arteries. Rib notching is still considered one of the most important signs of coarctation of the aorta, although it should not be considered pathognomonic. Coarctation does not always produce roentgenographically demonstrable rib notching, and rib notching is not always produced by coarctation of the aorta.

Bruwer and Pugh point out another good roentgenographic sign of coarctation which has been neglected. In 34 of 97 cases of coarctation of the aorta studied by these authors a notch was apparent in the left border of the shadow of the descending aorta, just above the level of the left main pulmonary artery, in the ordinary posteroanterior film of the chest. The notch represents the coarctate segment. Additional roentgenographic signs which may help in verifying the diagnosis are (1) inconspicuous ascending aorta, (2) dilatation of the ascending aorta, (3)

hypoplastic aortic arch, (4) visualization of the site of coarctation in the left anterior oblique view, (5) alterations of contour of the barium-filled esophagus, (6) prominence of the left border of the superior mediastinum in posteroanterior films, and (7) demonstration of the coarctate segment by means of angiocardiography or aortography. WEILAND, Grove City, Pa.

RESULTS OF NEUROSURGICAL TREATMENT OF OPTOCHIASMATIC ARACHNOIDITIS. MILLETTI and N. PAGLIERANI, Rev. oto-neuro-opht. **24**:294 (July) 1952.

Milletti and Paglierani report the results of neurosurgical treatment in 16 cases of optochiasmatic arachnoiditis during the course of 18 months in a hospital in Bologna. Of the patients 13 were women and 3 men; no age group was particularly involved. In one case complete blindness appeared overnight; in six cases there was rapid diminution of vision in a few days, and in nine a more progressive loss of vision developed over a period of weeks and months. The response to treatment was not as good in the cases with more rapid onset. In all cases there was a central or paracentral scotoma; in two cases there was impairment of the lower visual field, and in one case there was binasal hemianopsia. In most of the cases there was a concentric contraction of the visual field, with greater or less impairment of some of the quadrants. The fundi were normal in three cases, and in eight there was some edema around the nerve head, with pronounced papilledema in only one. Primary optic nerve atrophy was noted in 3 cases and secondary atrophy in 2 cases. Headache was the only significant extraocular complaint. The operative results were favorable in five cases, mediocre in six, and poor in five. The authors were unable to point to any factor which influenced prognosis after operation. The duration of the visual disturbance before operation, the age of the patient, and the condition of the optic nerves at operation had no effect on prognosis. N. SAVITSKY, New York.

UVEOMENINGITIS SYNDROME (RUBINO-CORAZZA SYNDROME). GIOVANNI P. ALLIANI and ROCCO GRAZIANO, Riv. oto-neuro-oftal. **28**:139 (March-April) 1953.

Alliani and Graziano report what was considered to be a virus infection of the uveal tract in both eyes and of the leptomeninges, described by Rubino and Corazza in 1941. An Argentinian aged 40, single, had sudden onset of headache and fever. Severe headache persisted for five days, with occasional vomiting. The fever cleared up on the third day. Eight days after the onset vision became impaired. The patient was admitted to a hospital. He was afebrile, and the physical findings were entirely normal. Neurologic examination showed a stiff neck and a bilateral Kernig sign. Ocular examination showed pericorneal injection and anterior uveitis. Slit-lamp microscopy revealed exudate in the posterior surface of the cornea. The fundi showed distended retinal veins, hyperemia of the disks and edema of the retinas. Vision was diminished, being 1/10 in each eye. A lumbar puncture yielded fluid with 21.6 cells per cubic millimeter, a positive Pandy reaction, a negative Wassermann reaction, and a total protein content of 36 mg. per 100 cc.; the colloidal gold curve was 0123000000. The patient was treated with chlortetracycline (Aureomycin), salicylates, thiamine chloride, and artificial fever.

On reexamination three months later the patient was found to be normal neurologically. Four months later the ocular status was normal. Lumbar puncture then showed 2 cells per cubic millimeter, negative Pandy and Wassermann reactions, and a total protein content of 22 mg. per 100 cc. N. SAVITSKY, New York.

Diseases of the Brain

ACUTE RESPIRATORY FAILURE IN MULTIPLE SCLEROSIS AND ITS MANAGEMENT. T. C. GUTHRIE, J. F. KURTZKE, and L. BERLIN, Ann. Int. Med. **37**:1197 (Dec.) 1952.

Guthrie and his co-workers describe four patients who had clinical courses typical of multiple sclerosis. Each had an episode of severe respiratory failure in the course of the illness. The respiratory dysfunction was clearly attributable to ventilatory insufficiency and was characterized by painless dyspnea, tachypnea, and tachycardia.

The patients with respiratory failure had certain distinctive features. Each manifested quadriparesis and depression of thoracic excursions as part of a rapid change in their neurological status. All four were spastic at one time, but two later became flaccid. Three patients had a

segmental level of sensory loss. The authors note that dyspnea, tachycardia, and respiratory depression were present in each case, even before there was the complete development of quadriparesis, and that paresis of the extremities increased in two cases after respirator therapy was instituted. Hence mild dyspnea, tachycardia, and tachypnea in multiple sclerosis may portend the further development of quadriparesis and potentially fatal respiratory depression. The measurements of vital capacity and arterial oxygen saturation are important in the early recognition of ventilatory failure in acute multiple sclerosis.

Two of these four patients died. In both the fatal cases there was late recognition of ventilatory insufficiency, and treatment with oxygen and tracheal aspiration was not adequate to compensate for the paralysis of the muscles of respiration. In both the patients who lived, respiratory failure was recognized early, and they were managed in Drinker respirators for 7 and 16 days, respectively.

ALPERS, Philadelphia.

CONVULSIONS FOLLOWING USE OF ASTEROL DIHYDROCHLORIDE. W. N. FEATHERSTONE, J. A. M. A. **150**:1006 (Nov. 8) 1952.

Featherstone describes an infant aged 4 months to whose skin large quantities of Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) dihydrochloride had been applied by an overzealous mother for the treatment of ringworm. After 10 days of treatment convulsions occurred. Physical examination, including neurological and ophthalmoscopic examinations, revealed no other abnormality.

Convulsions cleared after the cessation of medication, but at the time of this report the child had not regained his usual alertness. The pattern of this baby's course indicated intoxication as a cause of the convulsions. The author advises caution in the use of Asterol dihydrochloride to prevent excess absorption of it by small children and infants.

ALPERS, Philadelphia.

TENSION HEADACHE. A. FRIEDMAN, N. DE SOLA POOL, and T. J. C. VON STORCH, J. A. M. A. **151**:174 (Jan. 17) 1953.

In this presentation the authors discuss a group of patients with tension headache—their mechanism, characteristics, diagnosis, and response to therapy. They believe the term tension headache should be limited to head pain occurring in relation to constant or periodic emotional conflicts, which may be conscious or unconscious. Tension headaches have no prodromata, are usually bilateral, occipital, or frontal, and may be accompanied by a variety of associated signs, including anxiety, nausea, and vomiting. Frequency and duration are variable.

In this study 400 consecutive cases of tension headache were analyzed according to the following factors: age; sex; presence of prodromal signs; location, frequency, intensity, and duration of headaches; associated symptoms; family history; precipitating factors, and response to symptomatic treatment.

The authors found that tension headache responds to placebos in over 50% of the cases. The best symptomatic relief was obtained with analgesics and sedatives (in 64%). The best prophylactic results were obtained by psychotherapy (58%). They point out that the patient-physician relationship is of prime importance in the treatment of such headache.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

CARDITIS IN POLIOMYELITIS: ANATOMIC STUDY OF 35 CASES AND REVIEW OF LITERATURE. T. E. LUDDEN and J. E. EDWARDS, Am. J. Path. **25**:357 (May) 1949.

The 35 cases investigated by Ludden and Edwards represent all the cases of poliomyelitis in which necropsy was performed at the Mayo Clinic from Aug. 2, 1925, to Dec. 11, 1946, inclusive, and in which the hearts were available for study. Myocarditis was observed in 14 of 35 cases of fatal poliomyelitis. There was one case each of acute vegetative endocarditis and endarteritis of a patent ductus arteriosus. Since the cardiovascular lesions in these cases were otherwise unsatisfactorily explained, poliomyelitis virus must be considered as possibly causative. Proof of cardiovascular lesions in acute poliomyelitis virus will depend on demonstration of

the virus in the lesions and the experimental production of such lesions. The diagnosis of myocarditis complicating acute poliomyelitis is seldom made during life, but it should be suspected in every case of severe acute poliomyelitis. Myocarditis, as observed in this series of cases, was usually severer and proportionately commoner in adults than in young children. There was no specific correlation of type of paralysis—bulbar or spinal—with the presence or absence of myocarditis. The actual role of myocarditis as a cause of sudden death in acute poliomyelitis could not be determined in this study, except in one case, with a perforation of the right atrium. Three of the six patients who died suddenly were found to have myocarditis, but all these patients had bulbar involvement, which might have explained their sudden deaths. J. A. M. A.

FACIAL PAIN FROM ELONGATED STYLOID PROCESS. T. E. DOUGLAS JR., A. M. A. Arch. Otolaryng. **56**:635 (Dec.) 1952.

Since presentations by Eagle and Fritz, the symptomatic styloid process has become recognized as an entity to be sought in routine examinations. The usual symptoms of an elongated styloid process are dysphagia, frequent swallowing, increased salivation, fullness in the throat or a sore throat, a feeling that food has lodged in the throat, and sharp, lancinating pains in the ear. Dr. Eagle has stated that the carotid syndrome and migraine headache may be produced by elongation of the styloid process.

Douglas presents another case of the syndrome, with pain radiating along the third division of the trigeminal nerve. The patient, a woman aged 31, presented an outstanding, chief complaint of severe, sharp, excruciating pain commencing over the left parotid region, which radiated along the ramus and body of the left side of the mandible and, to a less degree, over the cheek and digastric regions on the left. The pain was accentuated by chewing and by opening the mouth. Sometimes the patient suffered severe lancinating pains in the left ear. There was a history of painful swallowing of almost two years' duration. These symptoms varied with the weather; they were worse on damp cold days and absent during warm dry periods.

After several extractions by her dentist failed to produce relief, she was seen by three nose and throat specialists. Each physician dismissed her from his service with a report of normal physical findings, and she was told to "stop worrying."

When she was examined one year later, nothing abnormal was noted until digital examination of the oral cavity was done. As the palpating finger was pressed against the left tonsillar fossa, a hard, pointed, and rather immobile object was encountered near the anterior pillar at the level of the superior alveolar ridge. Reproduction of the pain along the face, in the ear, and in both jaws occurred with lateral displacement of this hard, pointed object. A diagnosis of symptomatic elongated styloid process was made.

The report of the roentgenologist was nonspecific, although he thought that a shadow might be the styloid process or its ossified stylohyoid ligament. Postoperative films failed to show this area of contrast; so the report was made more definitive.

The styloid process was removed at operation, and the patient was discharged on the fourth postoperative day. She was asymptomatic for 2½ weeks. She then had a 10- or 11-day period of tingling, which followed the facial distribution of the preoperative plan. Since then she has been asymptomatic.

Douglas stresses the importance of palpation with the finger in examining for an elongated styloid process. This syndrome is probably commoner than the literature indicates.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

DIABETIC NEUROPATHY AND ITS PROGNOSIS. S. H. EPSTEIN, Neurology **1**:228 (May-June) 1951.

A review of the literature by Epstein gives little indication of how neuropathy arises in diabetes, but arteriosclerosis appears to be a contributing factor from both the clinical and the pathologic standpoint. This applies to the true neuritic type of neuropathy, as well as to the so-called degenerative, or ischemic, type.

In the present study of 50 cases of diabetic neuropathy, consideration is given to the clinical characteristics of the disease, and an evaluation of the possible factors in the production of the neuropathy is attempted, with particular reference to the role of vascular disease.

Epstein found that diabetic neuropathy is best classified into two types on the basis of prognosis: (1) that associated with arteriosclerosis, and (2) that without demonstrable evidence of vascular disease. The latter type carries a good prognosis, and the former, a distinctly poor prognosis. There is little, if any, improvement in cases in which arteriosclerosis is present, and usually there is progression of the symptoms. The patients without arteriosclerosis are usually under 40 years of age, in contrast to the older age of patients whose neuropathy is associated with arteriosclerosis. Poor control of diabetes in either type plays a role in the precipitation or aggravation of neuropathy.

ALPERS, Philadelphia.

INTRASACRAL MENINGOCELE CAUSING BACKACHE AND SACRAL NERVE PAIN: REPORT OF CASE. G. S. BAKER and J. H. WEBB, Proc. Staff Meet., Mayo Clin. **27**:231 (June 4) 1952.

Meningoceles situated entirely within the sacral canal are unusual. They may produce backache, with sacral or sciatic pain. Baker and Webb describe such a condition in a woman aged 28. She had had frequent low backache for about 10 years. For about six months pain had become more intense and had extended from the lumbosacral region to the posterior portions of the thighs. Conservative measures failed to relieve her symptoms.

Examination revealed moderate tenderness to percussion over the lumbosacral region, slight limitation of movement of the lumbar portion of the spinal column, absence of ankle reflex on the left, and a very weak ankle reflex on the right. Roentgenograms revealed thinning of bone about the sacral canal at the second, third, and fourth sacral segments. Myelographic studies disclosed an intrasacral sac, 4.5 cm. in diameter, situated at the second and third sacral segments.

A laminectomy over the second, third, and fourth sacral segments on the left was performed, and a large cyst containing clear, colorless fluid was disclosed. The cyst was freed from the underlying sacral roots and removed. The sacral nerve roots had been compressed anteriorly and greatly flattened. The patient made an uneventful recovery, and her condition was considerably ameliorated at the time of her discharge.

The authors believe that the long history of backache in this case, the thinning of the bone about the sacral canal, and the marked compression of the sacral nerve roots suggest that the origin was a congenital defect at the termination of the dural cul-de-sac, with the development of a meningocele that protruded in a caudad direction.

ALPERS, Philadelphia.

ACUTE POSTEMOTIONAL PORPHYRIA WITH EXOPHTHALMOS, EXTENSIVE PARETIC SYNDROME, AND MENTAL DISTURBANCE. L. MARCHAND and J. AJURIAGUERRA, Encéphale **38**:113, 1949.

The authors report the case of a married woman aged 32, who was admitted to the hospital in February, 1948. The family history was noncontributory. She had had a bout of jaundice in 1946. In January, 1948, she was nearly run over by an automobile while riding along a road on her bicycle. She was greatly frightened and upset by the incident but continued on her way. That night she vomited; her menses stopped, and abdominal pains appeared. During February there appeared simultaneously exophthalmos and a progressive pigmentation of her skin, most prominent on the face and neck. The anorexia, vomiting, pain, and anxiety continued, and she was rehospitalized in a psychiatric institution as having a reactive depression with anorexia. Examination revealed marked generalized tremors of the anxiety type, exophthalmos, pigmentation, and pronounced general muscular weakness. The reflexes were normal; the liver was slightly tender, and the temperature, pulse, and blood pressure were normal. As the asthenia progressed, so did the paresis. The patient could scarcely lift a leg or turn in bed. One morning, dark-red urine was noted, and the laboratory reported porphyruria. By early March the patient was in a state of generalized paretic weakness, with severe hyperesthesia of the skin of the extremities and muscles, a bilateral Lasègue sign, absence of the knee and ankle reflexes on the right and decrease in their strength on the left, and decreased reflexes in the upper extremities. There was no paralysis of the facial muscles. Touch, temperature, pain, and position sensibility was diminished, but the Babinski sign was not elicited. The patient became

somnolent by day and delirious and confused at night. Vigorous treatment with liver extract, vitamin B, etc., was instituted, with no improvement. Her mental confusion increased, and generalized fibrillations, particularly of the tongue, appeared. Episodes of dyspnea and confusion became more pronounced. She died of suffocation on March 9, 1948. The blood and spinal fluid had been normal.

Autopsy showed acute hepatitis with infiltration with melanin; the kidneys were the site of toxic interstitial nephritis. The pancreas showed acute hemorrhagic steatonecrosis; the spleen, infiltration with melanin. The gastric mucosa was hemorrhagic, and the thyroid was in a hyperfunctional state. The brain showed acute lesions of the ganglion cells of the cortex, gray nuclei, medulla, and cerebellum; the spinal ganglia were affected, as were the radicular cells of the cord. The adrenal glands were sclerotic, and the ovaries were polycystic.

ZINKIN, New York.

HYPERTROPHIC INTERSTITIAL NEURITIS OF DEJERINE-SOTTAS AND VON RECKLINGHAUSEN'S DISEASE. J. C. ORTIZ DE ZARATE and F. RUGGIERI, Prensa méd. argent. **87**:2185 (Sept. 15) 1950.

A white man aged 38 was admitted to the hospital on Aug. 10, 1949, with a history of recurring pain in both thighs and buttocks and the lower back for seven years, each attack lasting two or three days. For the last five years his gait had been unsteady, and clumsiness of the hands was definitely worse with the eyes closed; there was also weakness in the lower limbs for the same period, which was severe on exposure to cold. The patient reported that he felt electric-like sensations throughout his body on wetting his hands in cold water. Since his childhood he was aware of thinness of his arms and legs and of spots on his body. For about a year he burned himself without being aware of it. At the age of 32, after a mild head injury, he fell, with complete quadriplegia, from which he recovered in a few moments. The next day he had similar transitory weakness of all four extremities after a minor head injury. At the age of 12 he had had a severe occipital injury with persistent headaches. About the same time he sustained an injury to the lumbar region, without sequelae.

Examination showed cafe-au-lait spots over the entire body, as well as nontender subcutaneous nodules; there were prounounced palpable enlargement of the peripheral nerves and some irregularities along these nerves. Waxy rigidity was present in all four limbs and myoclonic twitchings were seen in the thighs and calves. Both rigidity and twitching were less evident in warm surroundings. There were atrophy, predominantly distal, of the musculature of the extremities, paralysis of the right external rectus, and hyperreflexia of the upper limbs. The knee jerks were equal and active; the ankle jerks were relatively less active, with the Babinski sign positive on the left and inconstant on the right. The abdominal reflexes were active. There were diminished superficial sensation in all four limbs, most pronounced acrally, and patchy involvement of pain and temperature sensibility over the trunk. Vibration sense was impaired over the entire body except in the clavicles and ribs. The Romberg sign was positive, especially when the patient was cold. Ataxia was present in the upper and lower limbs, being worse with the eyes closed.

Cold agglutination tests were positive in a dilution of 1:2,048; the Donath-Landsteiner test (autohemolysis to cold) gave a negative result. There was diminished reaction of the muscles in the lower extremities to the galvanic and faradic currents but no reaction of degeneration. Actual examination of the ulnar nerve showed it to be as large as the sciatic nerve. Peripheral neurography also confirmed the presence of an enlarged nerve.

This patient had Dejerine-Sottas neuropathy (progressive hypertrophic interstitial neuropathy) and Recklinghausen's disease. Pyramidal tract signs suggest the possibility of interstitial neurofibromas. A positive reaction to the cold agglutination test has never yet been described in either of these diseases. The authors do not think the association of the two diseases is accidental. The Schwann cells, which were hyperplastic in both diseases, are the peripheral analogues of the oligodendroglia cells. Both these diseases are manifestations of oligodendrogliomatosis. The authors express no opinion as to the possible relation of the positive cold agglutination test to the two diseases which were present in the same patient.

N. SAVITSKY, New York.

Cerebrospinal Fluid

CEREBROSPINAL FLUID CHANGES IN MULTIPLE SCLEROSIS. F. LOTMAR, Schweiz. Arch. Neurol. u. Psychiat. **66**:193-216, 1950.

A man aged 56 had been subject to attacks of headache for six years. The headaches had been much severer during the past two or three years, and a disturbance of gait, first noted four years before, had been more pronounced the past two years. The pupils reacted somewhat sluggishly to light; the right optic disk was a trifle pale, and central vision was impaired on the right. Ataxia of the legs was more pronounced on the right than on the left, and the patellar reflex was more active on that side. Neither the abdominal nor the cremasteric reflexes could be elicited, and the Babinski reflex was present bilaterally. The initial pressure of the spinal fluid was "somewhat higher than 150 mm. of water." The concentration of total protein, as determined by the Kjeldahl method, was 278.25 mg. per 100 cc.; the respective values for albumin and globulin were 202.70 and 75.55 mg. per 100 cc., giving an albumin-globulin ratio of 2.68. Colloidal gold and mastic tests yielded positive reactions of moderate degree in the first five tubes. A diagnosis of intracranial expanding lesion was made, but the patient refused to have a ventriculography made. It was subsequently learned that he gradually lost his vision prior to his death, eight years later. Autopsy revealed typical lesions of multiple sclerosis in both the brain and the spinal cord, the plaques being particularly numerous and extensive in the subependymal portions of the cerebral hemispheres.

Concentrations of total protein in the spinal fluid materially in excess of 100 mg. per 100 cc. not only are extremely rare in cases of multiple sclerosis, but have never been reported in anatomically verified cases. Concentrations greater than 50 mg. per 100 cc. are not common. In a case reported by Seuberling (*Nervenarzt* **13**:359, 1940), and included later in Schaltenbrand's monograph (Die multiple Sklerose des Menschen, 1943) the concentration of total protein in fluid obtained by lumbar puncture was 510 mg. per 100 cc. (7.0 mg. in the original report) but almost normal (1.3 mg.) in fluid obtained by cisternal puncture. Six days later, the concentration in fluid obtained by lumbar puncture was only 48 mg. per 100 cc. (1.4 mg. in the original report). [In a clinically typical case of multiple sclerosis studied by the reviewer, the concentration of total protein in the spinal fluid was 325 mg. per 100 cc. when the patient was first examined and 35 mg. per 100 cc. four months later. Minimal pleocytosis and a colloidal gold curve of the dementia paralytica type were demonstrated on both occasions.]

DANIELS, Denver.

Treatment, Neurosurgery

A ROENTGEN EVALUATION OF VERTEBRAL FRACTURES RESULTING FROM CONVULSIVE SHOCK THERAPY. HAROLD J. ISARD, Am. J. Roentgenol. **68**:247 (Aug.) 1952.

Isard reports on 30 cases of fracture of the spine following shock therapy with electroshock and/or insulin shock. In all these cases he made routine films before and after the shock therapy and followed all the patients at least two years by means of serial films. Fracture of several of the thoracic vertebral bodies is the rule, although a single body is sometimes fractured. The most commonly fractured thoracic vertebral bodies are the fourth, fifth, and sixth. Fractures of the lower thoracic and the lumbar vertebrae occasionally occur. Isard has not observed fracture of the first thoracic or of the cervical vertebrae.

As a rule, the fractures consist merely of a slight depression in the middle portion of the upper surface of the vertebral body. A narrow zone of increased density, caused by impaction of bone, is seen just below the upper surface of the body. A fracture line usually is not visible, and there is no wedging of the vertebral body. Isard believes, as Brailsford does, that the fractures are caused by "disk repercussion," rather than by acute flexion. These fractures usually heal promptly and leave no permanent disability. When the fracture has healed, there is usually residual deformity of the superior surface of the vertebral body. Quite often there is narrowing of the intervertebral disk space at that level.

Isard believes that the complication of vertebral fracture in convulsive shock therapy is usually not serious and that the average fracture does not require specific therapy. Old fractures, arthritis, scoliosis, and kyphosis are not considered contraindications to shock therapy.

WEILAND, Grove City, Pa.

Encephalography, Ventriculography and Roentgenography

FORAMINA PARIETALIA PERMAGNA. KNUD H. KRABBE, Arq. neuro-psiquiat. **10**:328 (Sept.) 1952.

Parietal foramina through which emissary veins pass are sometimes symmetrically dilated. About 50 cases have been recorded in the literature. A postman aged 44 was admitted to a Copenhagen hospital for treatment of histamine headache, a labyrinthine disorder, and myalgia of the neck. A roentgenogram of the skull showed round symmetrical defects in the parietal bones, each about 2 cm. wide. These defects were very near each other and at one point seemed to be connected. The edges of the defects were smooth. There were palpable depressions in the skull at the site. The floor of these palpable depressions was firm, as though formed by a layer of connective tissue but not bone. The skin and hair covering the depression were normal. A sister, aged 34, had similar skull defects. The defects in the sister were larger and fused with each other. These parietal foramina are considered vestiges of the so-called parietal eye in lower animals.

N. SAVITSKY, New York.

Congenital Anomalies

CLINICAL AND ROENTGENOLOGICAL MANIFESTATIONS OF THE KLIPPEL-FEIL SYNDROME. M. I. SHOUL and M. RITVO, Am. J. Roentgenol. **68**:369 (Sept.) 1952.

Shoul and Ritvo discuss the existing literature concerning the Klippel-Feil syndrome and add eight cases to the literature. The Klippel-Feil syndrome is characterized by fusion of two or more of the cervical vertebrae. Feil originally described three types of the condition: (1) that with complete fusion of the cervical portion of the spine, (2) that with partial coalescence of the cervical segments, and (3) that with reduction of the number of cervical vertebrae and fusions and anomalies in other parts of the spinal column.

Clinically, the syndrome is manifested by shortening and limitation of mobility of the neck, lowering of the hair line on the neck, and, in extreme cases, an appearance of implantation of the head on the chest. Confirmation by means of roentgenograms is necessary to establish the diagnosis. In most cases the diagnosis is made by roentgenograms alone, since the external appearance of the patient is not changed enough to suggest the abnormality.

The cause of the abnormality is not known. The authors discuss various embryological theories. In general, the prognosis is good, and the disease is compatible with long life. Frequently other congenital anomalies occur with it and may affect the prognosis. Shoul and Ritvo believe that patients with the Klippel-Feil syndrome are particularly susceptible to fracture of the cervical vertebrae and should take precautions to avoid trauma to the neck. Two of their eight patients sustained fractures, resulting in the sudden death of one.

The Klippel-Feil syndrome may produce neurologic symptoms and signs in some patients. Symptoms suggesting pressure on the cervical portion of the spinal cord and on the cervical nerve roots in patients having short necks should suggest the diagnosis. One of the authors' patients presented weakness of the right arm and leg, hemiatrophy, and other abnormal neurologic findings.

WEILAND, Grove City, Pa.

SEASONAL INCIDENCE OF CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM. T. MCKEOWN and R. G. RECORD, Lancet **1**:192 (Jan. 27) 1951.

McKeown and Record report on the seasonal incidence of congenital malformations of the central nervous system, using as source material the annual reports of the Registrar-General for Scotland for seven years and 930 consecutive cases of malformations of the central nervous system in Birmingham over a seven-year period. They found that of all malformations reported as stillbirths or first-year deaths, about 70% and 40%, respectively, involved the central nervous system. The incidence of anencephalus was significantly higher in children born in the half-year from October to March than in those born in the half-year from April to September. Although the risk of anencephalus is higher for first than for later births, this factor was statistically ruled out as a likely cause for the seasonal variation. There was no evidence of seasonal variation in the incidence of spina bifida or hydrocephalus.

The authors also found that the incidence of malformations of the central nervous system in siblings born after the birth of a child with such a malformation is about six times the expected rate.

MADOW, Philadelphia.

News and Comment

AMERICAN ACADEMY FOR CEREBRAL PALSY

At the meeting of the American Academy for Cerebral Palsy, held in Fort Worth, Texas, Oct. 30 and 31, 1953, the following officers were elected: Dr. Meyer A. Perlstein, president; Dr. Lenox D. Baker, president-elect; Dr. Harry E. Barnett, secretary-treasurer.

THE AMERICAN ASSOCIATION OF PSYCHIATRIC CLINICS FOR CHILDREN FELLOWSHIPS

Fellowships offering specialized training in child psychiatry are available in a number of member clinics of The American Association of Psychiatric Clinics for Children which have been approved as training centers by the Association. The training begins at a third-year postgraduate level, with minimum prerequisites of graduation from medical school, a general or rotating internship, and a two-year residency in psychiatry—all approved. The majority of these clinics have also been approved individually by the American Board of Psychiatry and Neurology for a third year of training and for an additional year of experience.

Fellowship stipends are usually in line with United States Public Health Service standards, that is, approximately $3,600, as these stipends come mainly from the Public Health Service. Stipends sometimes are paid by state departments of mental health and the individual clinics; occasionally communities pay for the training of psychiatrists engaging to work in these communities at the end of their training. Special arrangements may be made occasionally to supplement the stipends by taking on other responsibilities locally, e. g., part-time work with the VA, consultation to social agencies. A limited number of training centers can offer higher stipends.

The office of The American Association of Psychiatric Clinics for Children acts as a clearing house for applicants. Application may be made through this office or directly to the individual clinics. In all cases, acceptance of applicants for training is by the individual training centers. For further information and for application forms, write to Miss Marion A. Wagner, Administrative Assistant, The American Association of Psychiatric Clinics for Children, 1790 Broadway, Room 916, New York 19.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

At the thirty-third annual meeting of the Association for Research in Nervous and Mental Disease, held in New York on Dec. 11 and 12, 1953, the following officers were elected for 1954: president, Dr. Rustin McIntosh; 1st vice-president, Dr. Walter Klingman; 2d vice-president, Dr. William S. Langford; secretary-treasurer, Dr. Clarence C. Hare; assistant secretary, Dr. Rollo J. Masselink.

The subject for the 1954 meeting will be "Psychiatry and Neurology of Childhood."

CONGRESS OF NEUROLOGICAL SURGEONS

The third annual meeting of the Congress of Neurological Surgeons convened in New Orleans at the Roosevelt Hotel from Nov. 12 to 14, 1953.

Sir Geoffrey Jefferson was the distinguished guest, and his papers included Changing Ideas on the Integration of the Brain, Trigeminal Tumors, and Chiasmal Gliomas. Dr. James R. Gay, White Plains, N. Y., was elected president, succeeding Dr. Nathaniel R. Hollister, of Dayton, Ohio. Dr. Daniel B. Sweeney, of Birmingham, Ala., was elected vice-president, and Dr. Bland W. Cannon, Memphis, was reelected secretary and treasurer. Members of the executive committee continuing in office were Dr. Frederick Rehfeldt, of Fort Worth, Texas, Dr. Donald B. Freshwater, of Pasadena, Calif., Dr. Raymond K. Thompson, of Baltimore, and Dr. Ira J. Jackson, of Galveston, Texas. Dr. Frank Ernest, of Toledo, Ohio, and Dr. Henry M. Suckle, of Madison, Wis., were newly elected to the executive committee.

NATIONAL TRAINING LABORATORY IN GROUP DEVELOPMENT

Based upon eight years of pioneering research and experience in the relatively new field of training leaders in the skills and understandings necessary for developing effective groups, the National Training Laboratory in Group Development will hold its usual three-week summer laboratory session at Gould Academy, Bethel, Maine. The dates will be from June 20 through July 10.

Approximately 125 applicants will be accepted for this session. Persons involved in problems of working with groups in a training, consultant, or leadership capacity in any field are invited to apply.

The NTLGD is sponsored by the Division of Adult Education Service of the National Education Association and by the Research Center for Group Dynamics of the University of Michigan, with the cooperation of faculty members from the universities of California, Chicago, and Colorado, Harvard University, the University of Illinois, the Ohio State University, Teachers College at Columbia University, the University of Texas, and other educational institutions. Its year-round research and consultation program is supported by a grant from the Carnegie Corporation of New York. For further information, write to the NTLGD, 1201 Sixteenth St., N.W., Washington 6, D. C.

UNITED CEREBRAL PALSY

Dr. H. W. Magoun, professor and chairman of the department of anatomy, University of California School of Medicine at Los Angeles, has been awarded the 1953 UCP-Max Weinstein award for "outstanding scientific achievement in cerebral palsy." Dr. Magoun won the award for his studies of factors promoting regeneration of nerve fibers in the central nervous system and of the physiology of the cerebral cortex and basal ganglia in relation to cerebral palsy.

The presentation was made at United Cerebral Palsy's fourth annual convention at the Hotel New Yorker on Nov. 14, 1953, by Dr. Sidney Farber, professor of pathology, Harvard Medical School at Children's Medical Center in Boston, who is volunteer chairman of UCP's Medical Advisory Board.

The UCP-Max Weinstein award consists of a plaque and $1,000 in cash, provided under the will of the late Mr. Weinstein, father of Mrs. Leonard H. Goldenson, whose husband is president of United Cerebral Palsy and president of American Broadcasting-Paramount Theatres, Inc.

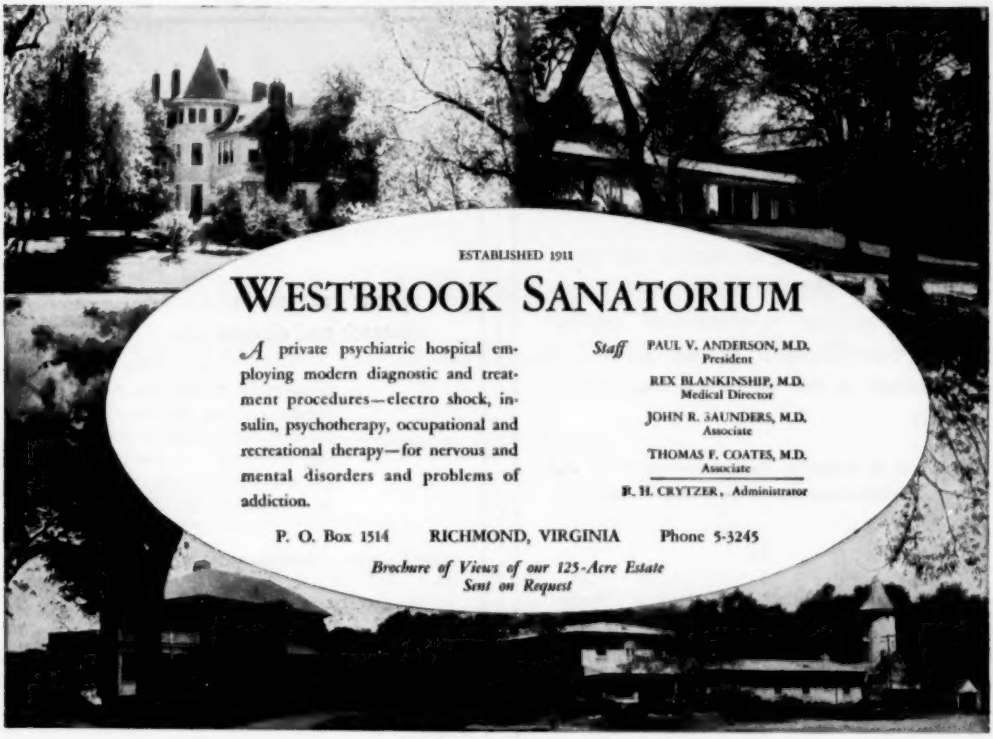
Previous winners of the award were Dr. Abner Wolf (1952), professor of neuropathology at Columbia University College of Physicians and Surgeons, New York, for his experimental work on toxoplasmosis, and Dr. Samuel P. Hicks (1951), New England Deaconess Hospital, Boston, who found that radiation and certain drugs given to prospective mothers cause damage to the brain tissue of their unborn and produce cerebral palsy in the young without damage to the mothers.

METROPOLITAN WASHINGTON DISTRICT BRANCH OF AMERICAN PSYCHIATRIC ASSOCIATION

Charter members of the Metropolitan Washington District Branch of the American Psychiatric Association as of Nov. 1, 1953, totaled 164, all of whom are members of the American Psychiatric Association. Officers are Dr. Henry P. Laughlin, president; Dr. Douglas Noble, vice-president; Dr. Seymour J. Rosenberg, secretary; Dr. Marshall DeG. Ruffin, treasurer.

WESTERN SOCIETY OF ELECTRO-ENCEPHALOGRAPHY

The 11th annual meeting of the Western Society of Electroencephalography will be held at Del Monte Lodge, Pebble Beach, Calif., March 7 and 8, 1954.



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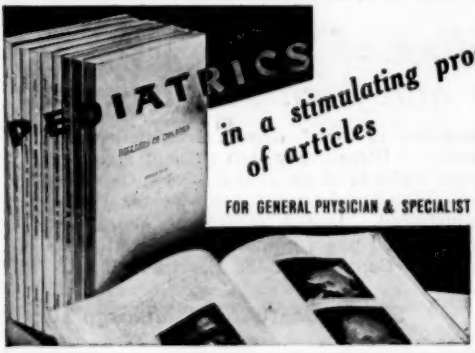

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